10

# United States Patent [19]

**Barnes et al.**

[11] **Patent Number: 4,721,723**

[45] **Date of Patent: Jan. 26, 1988**


[54] **ANTI-DEPRESSANT CRYSTALLINE PAROXETINE HYDROCHLORIDE HEMIHYDRATE**


[75] Inventors: **Roger D. Barnes**, Betchworth; **Marian W. Wood-Kaczmar**, Harlow; **Alan D. Curzons**, Worthing; **Ian R. Lynch**, Epsom; **John E. Richardson**, Harlow; **Philip C. Buxton**, Epsom, all of England

[73] Assignee: **Beecham Group p.l.c.**, Brentford, England



[21] Appl. No.: **922,530**

[22] Filed: **Oct. 23, 1986**

[30] **Foreign Application Priority Data**

Oct. 25, 1985 [GB] United Kingdom ..... 8526407
Oct. 25, 1985 [GB] United Kingdom ..... 8526408

[51] **Int. Cl.**[4] ..... **A61K 31/445; C07D 405/12**
[52] **U.S. Cl.** ..... **514/321; 546/197**
[58] **Field of Search** ..... 546/197; 514/321



[56] **References Cited**

U.S. PATENT DOCUMENTS

4,007,196 2/1977 Christensen ..... 546/197

OTHER PUBLICATIONS

*Chemical Abstracts*, 95:54664z (1981) [Goethert, M., et al., *Naunyn-Schmiedeberg's Arch. Pharmacol.* 1980, 313(1), 21–6].

J. B. Lassen, *Psychopharmacology*, 57, pp. 151–153 (1978).

J. B. Lassen, *European J. Pharmacol., 47, pp. 351–358 (1978).*

J. Lund et al., *Acta Pharmacol. et Toxicol.*, 44, pp. 289–295 (1979).

J. B. Lassen, et al., *Psychopharmacology*, 68, pp. 229–233 (1980).



*Primary Examiner*—Richard A. Schwartz
*Attorney, Agent, or Firm*—James F. Haley, Jr.; Alan M. Gordon



[57] **ABSTRACT**

The invention provides crystalline paroxetine hydrochloride hemihydrate, processes for its preparation, compositions containing the same and its therapeutic use as an anti-depressant.


**6 Claims, 3 Drawing Figures**

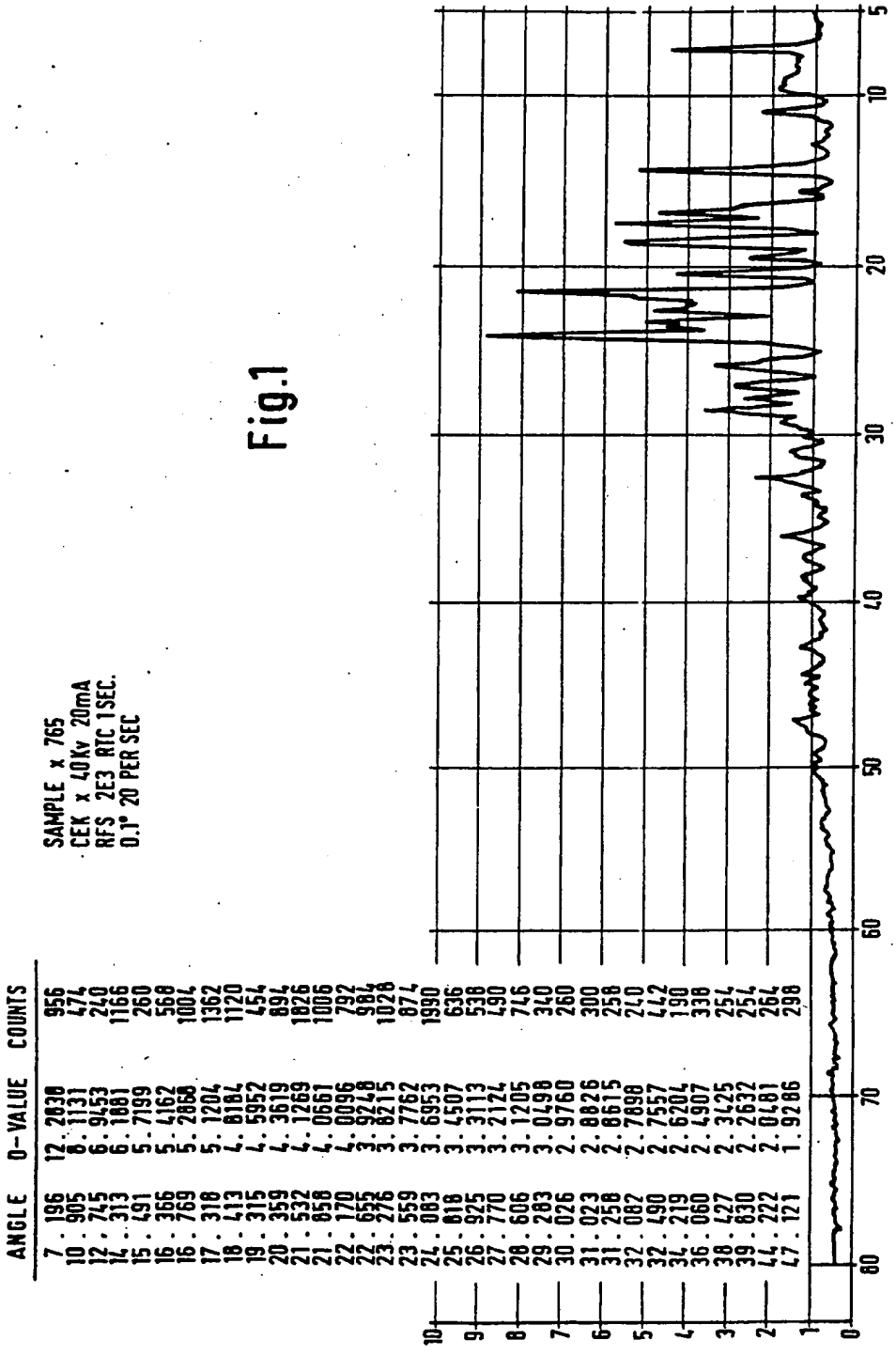

SAMPLE x 765
CEK x 40Kv 20mA
RFS 2E3 RTC 1SEC.
0.1° 20 PER SEC
ANGLE D-VALUE COUNTS
7.196 12.2838 956
10.905 8.1131 474
12.745 6.9453 240
14.313 6.1881 1166
15.491 5.7199 260
16.366 5.4162 568
16.769 5.2868 1004
17.318 5.1204 1362
18.413 4.8184 1120
19.315 4.5952 454
20.359 4.3619 894
21.532 4.1269 1826
21.858 4.0661 1006
22.170 4.0096 792
22.656 3.9248 984
23.276 3.8215 1028
23.559 3.7762 874
24.083 3.6953 1990
25.818 3.4507 636
26.925 3.3113 538
27.770 3.2124 490
28.606 3.1205 746
29.283 3.0498 340
30.026 2.9760 260
31.023 2.8826 300
31.258 2.8615 258
32.082 2.7898 240
32.490 2.7557 442
34.219 2.6204 190
36.060 2.4907 338
38.427 2.3425 254
39.830 2.2632 254
44.222 2.0481 264
47.121 1.9286 298
10
9
8
7
6
5
4
3
2
1
0
60
70
50
40
30
20
10
5

Fig.1

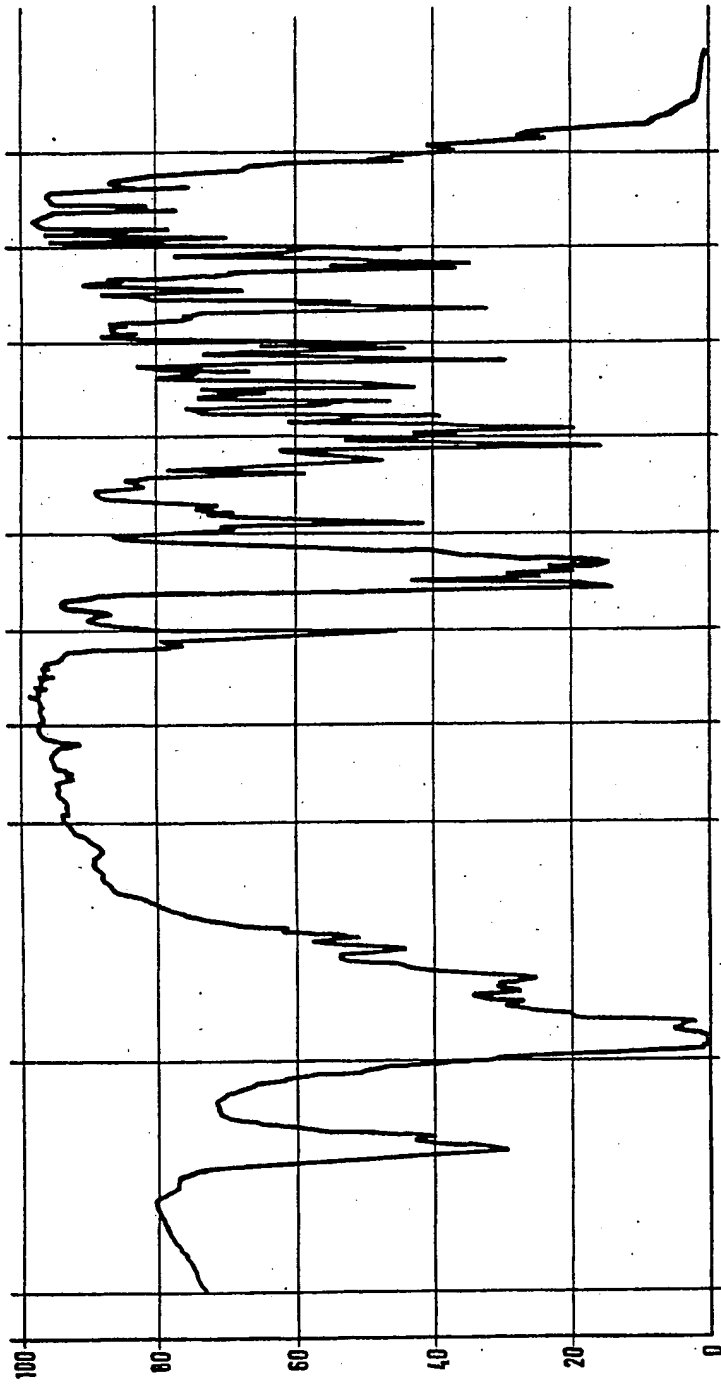

100
80
60
40
20
0
4000
3000
2000
1800
1600
1400
1200
1000
800
600
NUJOL MULL
SCAN 12 MINS
SLIT H

Fig.2

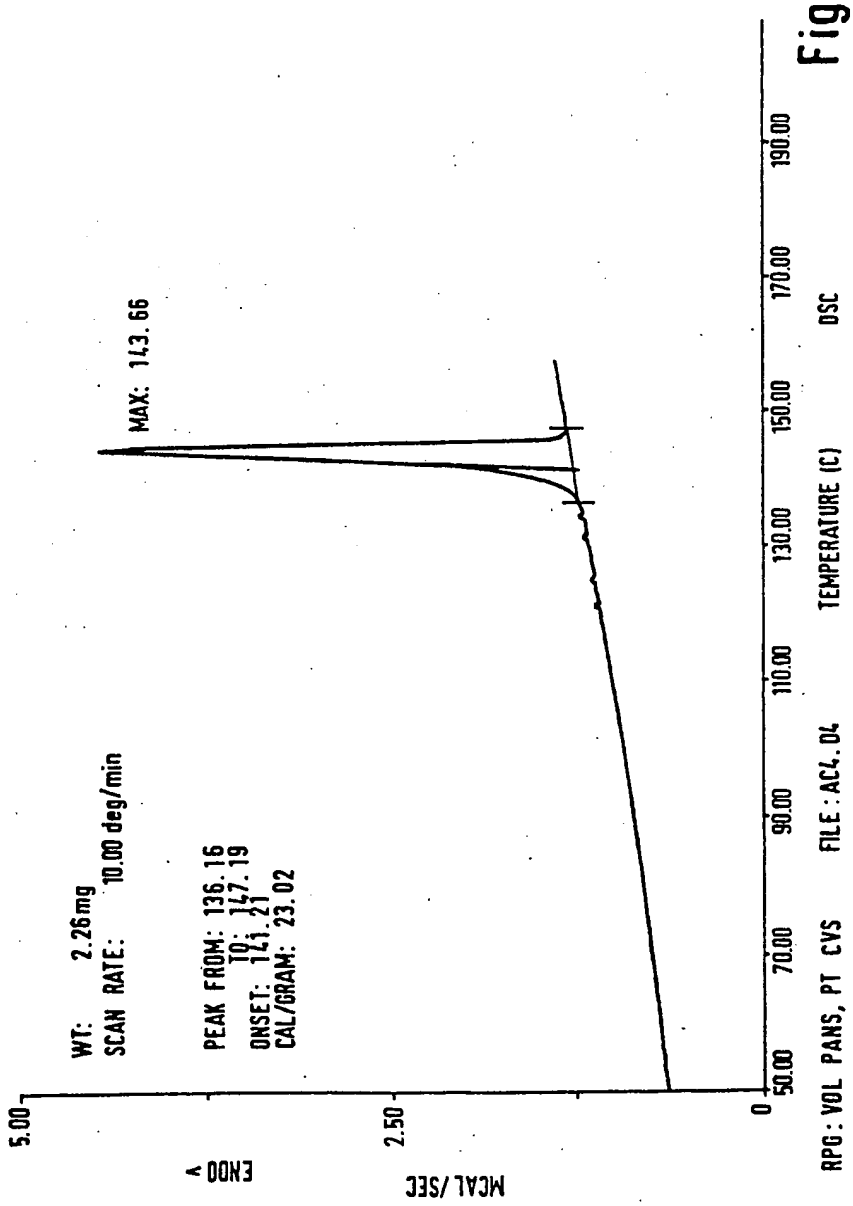
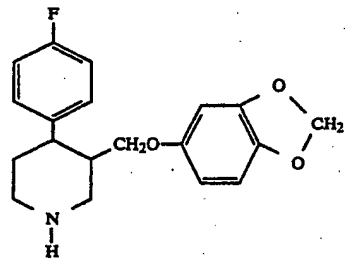

MAX: 143.66
WT: 2.26mg
SCAN RATE: 10.00 deg/min
PEAK FROM: 136.16
TO: 147.19
ONSET: 141.21
CAL/GRAM: 23.02
5.00
2.50
0
ENDO ▼
MCAL/SEC
50.00
70.00
90.00
110.00
130.00
150.00
170.00
190.00
TEMPERATURE (C)
RPG: VOL PANS, PT CVS
FILE: AC4.04
DSC

Fig.3

# ANTI-DEPRESSANT CRYSTALLINE PAROXETINE HYDROCHLORIDE HEMIHYDRATE

This invention relates to crystalline paroxetine hydrochloride, its preparation and its use as a therapeutic agent.

U.S. Pat. No. 4,007,196 discloses a class of compounds that are inhibitors of 5-hydroxytryptamine (5HT) uptake and thus of therapeutic use as anti-depressants. In Example 2 of the U.S. patent there is described the preparation of (−)-trans-4-(4'-fluorophenyl) 3-(3'4'-methylenedioxyphenoxymethyl)-piperidine of formula A:




(A)

In this specification the compound of formula A is referred to by its generic name of paroxetine.

Because of its basicity, it is preferred that paroxetine is used as a therapeutic agent in the form of an acid addition salt. In Example 2 of U.S. Pat. No. 4,007,196, paroxetine is obtained as the free base and then converted to its maleic acid salt.

The acetate salt of paroxetine has been used in most of the published experimental trials [for example, *Psychopharmacology*, 57, 151–153 (1978); *ibid.* 68, 229–233 (1980); and *European Journal of Pharmacology*, 47 (1978) 351–358]. There has also been limited use of the hydrochloride salt (in aqueous solution) [*Acta. Pharmacol. et Toxicol.* 1979, 44, 289–295]. However, the preparation of paroxetine hydrochloride has not been described in the literature.

In general, the hydrochloride salt of a basic compound is preferred for therapeutic use because of its physiological acceptability.

However for commercial use it is also important that the solid product should have good handling qualities.

We have found that amorphous paroxetine hydrochloride is a hygroscopic solid of poor handling qualities.

It has now been discovered that paroxetine hydrochloride can be produced in crystalline form in a manner reproducible on a commercial scale.

The present invention provides crystalline paroxetine hydrochloride hemihydrate as a novel material, in particular in pharmaceutically acceptable form.

Paroxetine hydrochloride hemihydrate is stable and non-hygroscopic. It is characterised by an X-ray powder diffractogram as shown in the accompanying FIG. 1. A typical Nujol infra-red spectrum (FIG. 2) and DSC profile (prepared using a 2.26 mg sample in a sealed container (FIG. 3) is also shown. Under extreme dessication conditions the bound water may be removed to give an anhydrous form, but on rehydration it rapidly reforms the hemihydrate.



The present invention also provides a process for producing crystalline paroxetine hydrochloride hemihydrate which comprises forming a solution of paroxetine hydrochloride and precipitating the crystalline form from solution.

The solution may be formed by dissolution of preformed paroxetine hydrochloride or by forming the hydrochloride in situ. The hydrochloride may be formed from a solution of paroxetine free base or a salt other than the hydrochloride by contacting it with hydrogen chloride.

For example a solution of hydrogen chloride, for example concentrated hydrochloric acid or an organic solvent saturated with hydrogen chloride may be added to a solution of paroxetine salt. Alternatively hydrogen chloride gas may be passed through the paroxetine (salt) solution.

Paroxetine base may be prepared by the procedure disclosed in U.S. Pat. No. 4,007,196. The U.S. Patent also gives procedures for preparing salts of paroxetine with various organic acids.

Typically, paroxetine hydrochloride may be obtained from an organic solution e.g. in toluene, of the free base by adding an appropiate amount of aqueous HCl.

In a procedure using a salt, paroxetine hydrochloride may be produced from a paroxetine $C_{1-5}$ carboxylate such as the acetate. The acetate may be obtained by reaction of acetic acid and paroxetine base in a non-polar solvent, such as diethyl ether or isopropyl ether. Alternatively it may be obtained from an aqueous solution obtained by extraction from a water-immiscible solvent e.g. toluene, ethyl acetate, by the addition of water and an appropriate amount of acetic acid.

Before conversion to the hydrochloride or crystallisation it may be desirable to remove impurities, since it has been found that some impurities may act as crystallisation inhibitors. However, the hemihydrate can even be obtained from relatively impure starting material, by means of seeding.

Paroxetine hydrochloride may be obtained as a crystalline hemihydrate by crystallization after addition of an aqueous solution of hydrochloric acid to a solution of paroxetine free base in water immiscible solvents e.g. toluene, or by crystallisation from water miscible solvents which do not form a solvate (e.g. IMS) after adding aqueous hydrochloric acid to a solution of the free base or by crystallising or recrystallising paroxetine hydrochloride from a solvent system containing water e.g. IMS/water. Alternatively the hydrochloride hemihydrate can be produced via another paroxetine salt by the addition of hydrochloric acid to an aqueous solution of the salt e.g. acetate.

In a preferred aspect, this invention provides paroxetine hydrochloride hemihydrate which is substantially pure.

The hemihydrate can be obtained by crystallisation from a range of solvents, although seeding may be necessary in some instances, after addition of aqueous HCl to a solution of the free base or another salt. Solvents which have been found suitable are toluene, water, IMS, lower alcohols such as ethanol and isopropanol and ethyl acetate. The same solvent range may be used for recrystallizatation.

In a particular aspect of the invention, paroxetine free base is synthesised in a particularly pure form which is especially suitable for use in the preparation of the crystalline paroxetine hydrochloride hemihydrate of the invention, even without seeding.

In the above mentioned U.S. Pat. No. 4,007,196, for the preparation of paroxetine (Examples 1 and 2), an N-methyl compound is reacted with phenyl chloroformate and the resultant compound is hydrolysed with potassium hydroxide.

One disadvantage of this process is that the solvent used during the hydrolysis step (methyl cellosolve) leads to the production of unwanted transesterification by-products.

We have now discovered that the purity of the final product can be improved by using a different solvent during the hydrolysis step, such as toluene. A further advantage is that the temperature at which the hydrolysis is carried out can thus be reduced, owing to the reduction in boiling point of the solvent used.

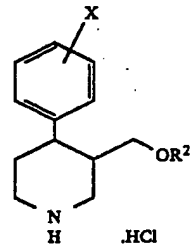
The pure paroxetine free base thus obtained can then be used for the preparation of crystalline paroxetine hydrochloride hemihydrate as set out above.

In a further aspect of the invention, crystalline paroxetine hydrochloride hemihydrate can be obtained by compressing crystalline paroxetine hydrochloride anhydrate.

In a still further particular aspect of the invention, paroxetine is synthesised directly as its hydrochloride salt, followed by crystallization as set out above.

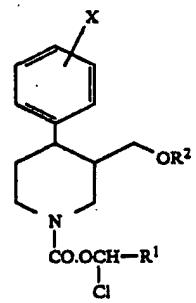
We have discovered a new process for the preparation of paroxetine and related compounds by a de-acylation procedure which advantageously provides the desirable hydrochloride salt directly.

Accordingly, the present invention provides a process for the preparation of a compound of formula I



I

in which $R^2$ represents an alkyl or alkynyl group having 1–4 carbon atoms, or a phenyl group optionally substituted by $C_{1-4}$ alkyl, $C_{1-6}$ alkylthio, $C_{1-6}$ alkoxy, halogen, nitro, acylamino, methylsulfonyl or methylenedioxy, or represents tetrahydronaphthyl, and X represents hydrogen, alkyl having 1–4 carbon atoms, $C_{1-6}$ alkoxy, $C_{1-6}$ trifluoroalkyl (preferably, trifluoromethyl), hydroxy, halogen, methylthio, or aryl($C_{1-6}$)alkyloxy (e.g., phenyl($C_{1-6}$)alkyloxy and benzyl($C_{1-6}$)alkyloxy) by de-acylating a compound of formula II

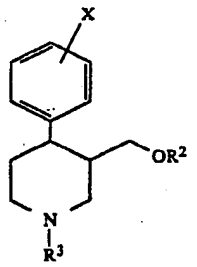


II

in which $R^1$ is a $C_{1-6}$ alkyl group and X is as defined for formula I.

The de-acylation may be achieved by heating the compound of formula II in a lower alcohol e.g. methanol. Preferably $R^1$ is a methyl group.

The de-acylation is advantageously carried out as the final step of a procedure for de-alkylating a compound of formula III

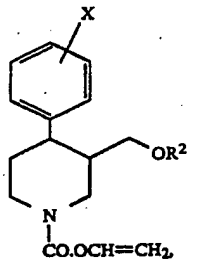


III

in which $R^3$ is a $C_{1-6}$ alkyl group and X is as defined for formula I.

The replacement of $R^3$ by $R^1$.CHClO.CO to convert the compound of formula III to the compound of formula II may be achieved by reacting the compound of formula III with α-chloro-ethyl chloroformate in a solvent such as dichloroethane or toluene.

Alternatively, the compound of formula III may be reacted with vinyl chloroformate in a solvent such as methylene dichloride or toluene to obtain the intermediate of formula IV



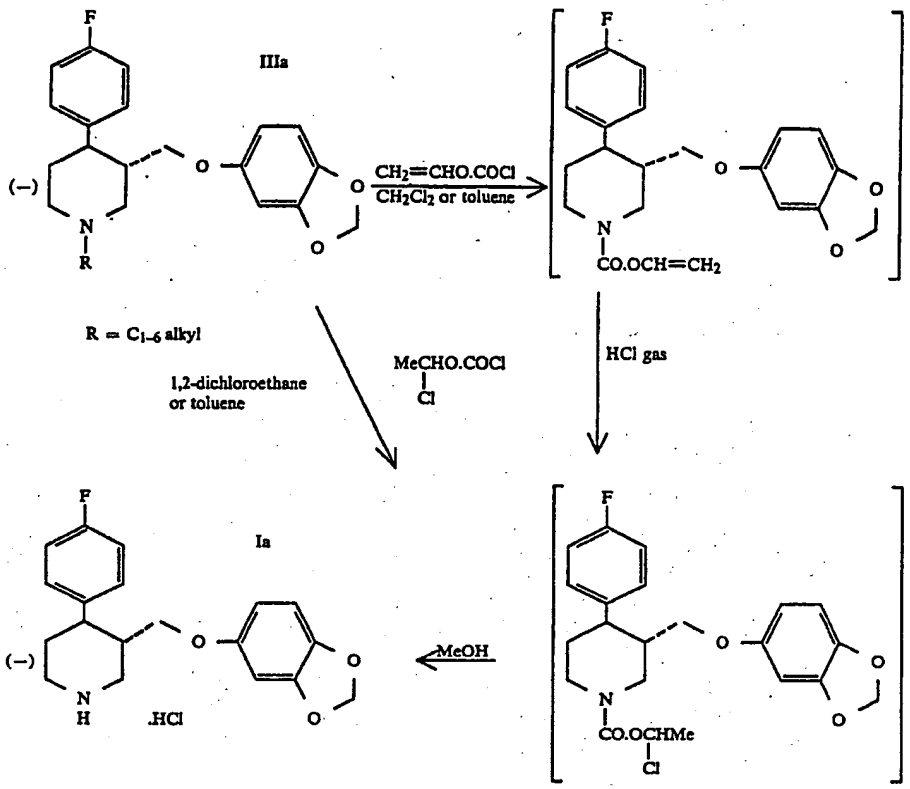
IV

wherein X and $R^2$ are as defined for formula I, which is then treated with HCl, preferably by passing HCl gas through the solution to obtain the compound of formula II.

An advantageous feature of this process is that the conversion of the compound of formula III into the compound of formula I can be carried out as a 'one-pot' process without isolating the intermediate of formula II or the intermediate of formula IV if the alternative route is followed.

The compounds of formula III may be prepared by the procedures set out in U.S. Pat. No. 4,007,196.

Advantageously, the process is used for the de-alkylation of a compound of formula IIIa to obtain paroxetine hyrochloride of formula Ia. This procedure is illustrated in the following reaction scheme.




The intermediates having the general formulae II and IV given above are novel compounds. They form part of the present invention, together with the processes for their preparation described herein. Compounds of formula I, which include paroxetine hydrochloride, are useful as antidepressants, as disclosed in U.S. Pat. No. 4,007,196, the disclosure of which is hereby incorporated herein by reference. In its preferred aspect the present invention provides paroxetine hydrochloride hemihydrate in pharmaceutically acceptable form.

The present invention also provides a pharmaceutical composition comprising crystalline paroxetine hydrochloride hemihydrate and a pharmaceutically acceptable carrier.

The compositions of this invention are usually adapted for oral administration, but formulations for dissolution for parenteral administration are also within the scope of this invention.

The composition is usually presented as a unit dose composition containing from 1 to 200 mg, more usually from 5 to 100 mg, for example 10 to 50 mg such as 12.5, 15, 20, 25 or 30 mg. Such composition is normally taken from 1 to 6 times daily, for example 2, 3 or 4 times daily so that the total amount of active agent administered is within the range 5 to 400 mg.

Preferred unit dosage forms include tablets or capsules.

The composition of this invention may be formulated by conventional methods of admixture such as blending, filling and compressing.

Suitable carriers for use in this invention include a diluent, a binder, a disintegrant, a colouring agent, a flavouring agent and/or a preservative. These agents may be utilized in conventional manner, for example in a manner similar to that already used for clinically used anti-depressant agents.

The invention also provides a method of treatment of depression in mammals including humans which method comprises administering an effective amount of pharmaceutically acceptable crystalline paroxetine hydrochloride hemihydrate.

The invention further provides pharmaceutically acceptable crystalline paroxetine hydrochloride hemihydrate for use in the treatment of depression.

The following Examples illustrate the invention. Examples 4 and 5 show the route formula III-IV-II-I, while Examples 6 and 7 show the route formula III-II-I. Temperatures are in ° C.

## EXAMPLE 1

(−)trans-4-(4'-Fluorophenyl)-3-(3'4'-methylenedioxyphenoxymethyl)-piperidine hydrochloride (Paroxetine hydrochloride) as hemihydrate ($\frac{1}{2}H_2O$)

(−)trans-4-(4'-Fluorophenyl)-3-(3'4'-methylenedioxyphenoxymethyl)-N-phenoxycarbonylpiperidine (18.5gms) was dissolved in toluene(275 mls). Potassium hydroxide (15.7 gms) was added. The mixture was refluxed for 2 hours with good agitation. The slurry was then cooled to 20° C. and the toluene washed once with water (275 mls).

To a solution of 13.5 g Paroxetine free base in toluene(300 ml) was added a small excess of either concentrated hydrochloric acid(5.2 ml)or dilute hyirochloric acid (150 mls of 0.35N)

The slurry was stirred at ambient temperature for 2 hours. The product was washed with toluene/water(25

ml 1:1 mixture) and dried at 50° C. to give paroxetine hydrochloride as the hemihydrate ($\frac{1}{2}H_2O$) containing 2.5% $H_2O$ with m.p. 128°–133° C., and IR consistent with that shown in FIG. 2.

## EXAMPLE 2

(−)trans-4-(4'-Fluorophenyl)-3-(3'4'-methylenedioxyphenoxymethyl)piperidine hydrochloride (Paroxetine hydrochloride) as hemihydrate ($\frac{1}{2}H_2O$)

To a solution of paroxetine free base obtained as described in Example 1 [23.5g] in toluene (ca.500 ml) was added 300 ml water. Acetic acid was added (6.4 g) and after 15 minutes stirring the lower aqueous layer containing paroxetine acetate was separated.

The aqueous layer was clarified by filtration through celite. Concentrated hydrochloric acid (15. Oml) was then added at ambient temperatures in the presence of paroxetine hydrochloride seed obtained as in Example 1 and the precipitated product stirred for 1 hour at ambient and then 2 hours at 0°–5° C.

The product was filtered, washed with water (2x40 ml)and dried at 50° C. to give paroxetine hydrochloride hemihydrate containing 2.6% $H_2O$ and consistent IR.

## EXAMPLE 3

Recrystallisation of Paroxetine hydrochloride to give the hemihydrate

(a) 0.50 g Paroxetine hydrochloride was recrystallised from 2.5 ml IMS (industrial methylated spirit) by dissolving at ca 60°–70° C. and cooling slowly to 20° C. then to 5° C. After seeding with crystals obtained as in Example 1, crystals of paroxetine hydrochloride hemihydrate were deposited and isolated in the normal way.

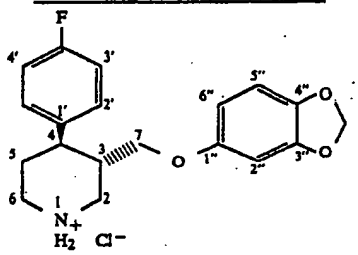
(b) 0.75 gm Paroxetine hydrochloride was recrystallised from 5. Oml water by dissolving at ca. 70° C. and cooling slowly to 20° C. After seeding with crystals obtained as in Example 1, crystals of paroxetine hydrochloride hemihydrate were deposited and isolated in the normal way.

## EXAMPLE 4

(−)-trans-4-(4'-Fluorophenyl)-3-(3',4'-methylene-dioxyphenoxymethyl)-piperidine hydrochloride

Vinyl chloroformate (6.42 ml) was dissolved in 2 ml dry methylene dichloride. The solution was cooled to 0° and the reaction flask purged with nitrogen. A solution of (−)-trans-4-(4'-fluorophenyl)-3-(3',4'methylenedioxy-phenoxy) methyl-N-methyl- piperidine (20 g) in 52 ml of dry methylene dichloride was added to the vinyl chloroformate solution over 30 minutes keeping the temperature below 0°. The mixture was allowed to warm to ambient temperature and stirred for 3 hours. The solution was then heated to reflux at 35° for a further 1 hour and cooled to −20°. Dry hydrogen chloride gas was bubbled into the solution for about 1 hour and the mixture allowed to stir at ambient temperature for 1 hour. Methanol (50 ml) was added to the solution and the mixture heated under reflux for 1 hour, followed by addition of charcoal (4.5 g) to the hot solution. Charcoal was filtered off after 10 minutes and the solvents removed in vacuo to give the crude product (21.4 g). The solid was dissolved in isoprOpyl alcohol (140 ml) and the solution filtered. The clear filtrate was cooled to 0° and seeded with crystals obtained as in Example 1 to allow the product to crystallise. After several hours at 0° the white solid was filtered off and the product slurried in water (30 ml), filtered off, washed with water and dried to give the hydrochloride salt as the hemihydrate (15.8 g, 74.1%).

$^1$H—n.m.r. (270 MHz, DMSO—$d_6$)



| δ | Multiplicity | Assignment | |
|---|---|---|---|
| 9.50 | s, br, exch. | $NH_2^+$ | 2H |
| 7.27 | dd, $^4J_{HF}$ = 6Hz | 2' | 2H |
| 7.17 | dd, $^3J_{HF}$ = 9Hz | 3' | 2H |
| 6.75 | d | 5" | 1H |
| 6.50 | d | 2" | 1H |
| 6.20 | dd | 6" | 1H |
| 5.94 | s | O—$CH_2$—O | 2H |
| 3.61 | dd | 7 | 2H |
| 3.53 | dd | | |
| 3.50 | m | 2 eq | 1H |
| 3.39 | d, br | 6 eq | 1H |
| 3.03 | ddd | 6 ax | 1H |
| 2.97 | dd | 2 ax | 1H |
| 2.90 | ddd | 4 | 1H |
| 2.58 | m | 3 | 1H |
| 2.10 | ddd | 5 ax | 1H |
| 1.85 | d, br | 5 eq | 1H |

## EXAMPLE 5

(−)-trans-4-(4'-Fluorophenyl)-3-(3',4'-methylenedioxyphenoxymethyl-piperidine hydrochloride

The reaction described in Example 4 was repeated substituting 100 ml of sodium dried toluene for 52 ml of dry methylene chloride. (−)-trans-4-(4'-Fluorophenyl)-(3+,4'-methylenedioxyphenoxymethyl)-N-methyl-piperidine (20 g) was converted to 16.5 g of the hydrochloride salt as the hemihydrate in a yield of 77.4%.

The $^1$H-n.m.r. spectrum was identical to that of the Example 4 product.

## EXAMPLE 6

(−)-trans-4-(4'-Fluorophenyl)-3-(3',4'methylenedioxyphenoxymethyl)-piperidine hydrochloride

(−)-trans-4-(4'-Fluorophenyl)-3-(3',4'-methylenedioxyphenoxymethyl)-N-methylpiperidine (10 g) and N,N,N',N'-tetramethyl-1,8-naphthalenediamine (0.3 g) were dissolved in 40 ml of dry 1,2-dichlorethane (EDC) and the solution cooled to −3°. α-Chloroethyl chloroformate (3.22 ml) in 5 ml of dry EDC was added to the cold solution over 15 minutes. The mixture was stirred for 20 hours at ambient temperature and then heated to reflux for 2 hours. Methanol (15 ml) was added to the solution and the mixture was refluxed for a further 2 hours. The mixture was washed with 20 ml of 1N hydrochloric acid and the phases were allowed to separate. The organic layer was evaporated to dryness and the residue was dissolved in isopropyl alcohol (60 ml). The hot solution was treated with charcoal (2 g) and alumina (1.5 g), stirred for 5 minutes and filtered hot. The clear solution was seeded with crystals obtained as in Example 1 and cooled to 0° for 18 hours. The white crystal-

line solid was filtered off and the wet product slurried in water (20 ml). The solid was filtered off, washed with water and dried to give the hydrochloride salt as the hemihydrate (7.9 g, 74.1%).

The $^1$H-n.m.r. spectrum was the same as that of the Example 4 product.

## EXAMPLE 7

(−)-trans-4-(4'-Fluorophenyl)-3-(3',4'-methylenedioxyphenoxymethyl)-piperidine hydrochloride

(−)-trans-4-(4'-Fluorophenyl)-3-(3',4'-methylenedioxyphenoxymethyl)-N-methylpiperidine (10 g) was dissolved in 45 ml of sodium dried toluene and the solution cooled to 5° . α-Chloroethyl chloroformate (3.22 ml) in 5 ml of dry toluene was added to the cold solution over 15 minutes. The mixture was stirred for 18 hours and methanol (15 ml) was added to the mixture. The solution was stirred for 12 hours at ambient temperature. The solvent was then distilled off in vacuo and the residue dissolved in hot isopropyl alcohol (60 ml). The hot solution was treated with charcoal (2 g) and alumina (1.5 g), stirred for 5 minutes, filtered, seeded with crystals obtained as in Example 1 and cooled to 0° for 18 hours. The white crystalline solid was filtered off, washed with a little isopropyl alcohol and the solid slurried in water (20 ml). The solid was filtered off, washed with water and dried to give the hydrochloride salt as the hemihydrate (9.8 g, 92%).

The $^1$H-n.m.r. spectrum was identical to that of the Example 4 product.

## EXAMPLE 8

(−)-trans-4-(4'-Fluorophenyl)-3-(3'4'-methylenedioxyphenoxymethyl)-piperidine hydrochloride (paroxetine hydrochloride)

Crude (−)-trans-4-(4'-fluorophenyl)-3-(3'4'-methylenedioxyphenoxymethyl) piperidine (0.341 kg) is dissolved in diethyl ether (3.5 liters) and stirred with aluminium oxide (ca. 0.3 kg) for about 3 hours. Charcoal (15 g) and filter aid (celite, 15 g) are added and the mixture filtered through a layer of aluminium oxide, the filtered solids being washed with more ether. To the combined ether solutions is added a mixture of acetic acid (66 ml) and ether whereupon the acetate of (−)-trans-4-(4'-fluorophenyl)-3-(3'4'-methylenedioxyphenoxymethyl) piperidine crystallises and is filtered off, washed with ether and dried.

The acetate salt is dissolved in isopropanol (2.4 liters) and treated with a mixture of concentrated hydrochloric acid (75 ml) and more isopropanol. After standing at about 0° C. for about 16 hours, the crystals of the hydrochloride salt containing isopropanol (needles) are filtered off and dried. The salt is stirred in distilled water (0.5 liters) for about 20 minutes, filtered off and dried, giving (−)-trans-4-(4'-fluorophenyl)-3-(3'4'-methylenedioxyphenoxymethyl) piperidine hydrochloride anhydrate (platelets m.p. 118° C.). IR(Nujol Mull) $\nu$890,1200, 1490, 3400, 3640 cm$^{-1}$.

Samples of the anhydrate were compressed at approximately 750 MNm$^{-2}$ and approximately 375 MNm$^{-2}$ for periods of about 2 minutes. The former underwent 45% conversion to the hemihydrate, whilst the latter remained unchanged.

Upon reexamining the samples after storage for several days, it was seen that the former sample had undergone complete conversion to the hemihydrate, whilst the latter sample had undergone about 50% conversion.

After a further week, the conversion of the latter sample was almost complete.

We claim:

1. Crystalline paroxetine hydrochloride hemihydrate.

2. Crystalline paroxetine hydrochloride hemihydrate in substantially pure form.

3. Crystalline paroxetine hydrochloride hemihydrate, having substantially the same X-ray diffractogram as set out in FIG. 1, substantially the same IR spectrum, in a Nujol mull, as set out in FIG. 2, and substantially the same DSC profile as set out in FIG. 3.

4. A process for the preparation of crystalline paroxetine hydrochloride hemihydrate, which process comprises forming a solution of paroxetine hydrochloride and crystallizing said hemihydrate from solution by precipitation or recrystallization.

5. An anti-depressant pharmaceutical composition comprising an effective anti-depressant amount of crystalline paroxetine hydrochloride hemihydrate and a pharmaceutically acceptable carrier.

6. A method of treatment of depression in mammals, which method comprises administering an effective amount of crystalline paroxetine hydrochloride hemihydrate.

* * * * *

```
=> s bioavaila?(l) sulfonat?

         28474 BIOAVAILA?
         63446 SULFONAT?
L12         32 BIOAVAILA?(L) SULFONAT?

=> s l12 and (methane or toluene)

         89958 METHANE
         85818 TOLUENE
L13          2 L12 AND (METHANE OR TOLUENE)

=> d bib abs 1-2


L13  ANSWER 1 OF 2  CA  COPYRIGHT 1999 ACS
AN   112:42350  CA
TI   Chronopharmacokinetic and bioequivalence studies of two formulations of
     trimipramine after oral administration in man
AU   Bougerolle, A. M.; Chabard, J. L.; Jbilou, M.; Dordain, G.; Eschalier,
A.;
     Aumaitre, O.; Gaillot, J.; Piron, J. J.; Petit, J.; Berger, J. A.
CS   Groupe Rech. Biodyn. Med., Lab. Chim. Anal., Clermont-Ferrand, F-63001,
     Fr.
SO   Eur. J. Drug Metab. Pharmacokinet. (1989), 14(2), 139-44
     CODEN: EJDPD2; ISSN: 0398-7639
DT   Journal
LA   English
AB   The bioavailability of 2 oral formulations of trimipramine, tablets and
     soln., was examd. in 12 healthy volunteers, in a crossover study.  Each
     formulation was administered in the morning after a fasted period, and in
     the evening after a meal, in order to evaluate the role of both
     administration time and food consumption on the plasma kinetic
parameters,
     under usual therapeutic conditions.  A high interindividual variability
of
     data was found.  First, the extent of bioavailability was identical for
     the 2 formulations but the rate of bioavailability seemed to be
different,
     with the oral soln., being more rapidly absorbed (tmax = 1.50 h).  The
     effect of administration time was more obvious for the soln. as shown by
a
     lower quant. absorption as well as a delay in time to reach the maximal
     concn.

L13  ANSWER 2 OF 2  CA  COPYRIGHT 1999 ACS
AN   104:74940  CA
TI   Absorption kinetics of dihydroergotoxine following oral administration to
     man
AU   Woodcock, B. G.; Rietbrock, N.; Loh, W.; Habedank, W. D.
CS   Dep. Clin. Pharmacol., Univ. Clin. Frankfurt, Frankfurt, D-6000, Fed.
Rep.
     Ger.
SO   Br. J. Clin. Pharmacol. (1985), 20(6), 603-9
     CODEN: BCPHBM; ISSN: 0306-5251
DT   Journal
```

LA English

AB The absorption characteristics of dihydroergotoxine **methane sulfonate** [8067-24-1] administered as an oral soln., tablet, or retard capsule were detd. in a randomized cross-over investigation in healthy males. The plasma concns. of dihydroergotoxine produced by the 3 prepns., measured using a specific and sensitive radioimmunoassay method over 24 h, exceeded 200 pg/mL for .apprx.5 h and decayed in a biphasic manner with a slowest measured half-life of 12-14 h. The retard capsule differs from the other 2 prepns. in having a low Cmax (50% of that recorded for the soln.) and a clearly defined plateau. The **bioavailability** of the retard capsule was similar to that for the soln. indicating that 1st-pass metab. is not significantly increased following a 3-fold prolongation in the absorption rate const. The 20-40% greater **bioavailability** of dihydroergotoxine soln. and retard capsule in comparison with the std. tablet may be due to a reduced contact time with gastric secretions achieved by means of rapid absorption from the stomach (soln.) or delayed release at pH 1.5 (retard capsule).

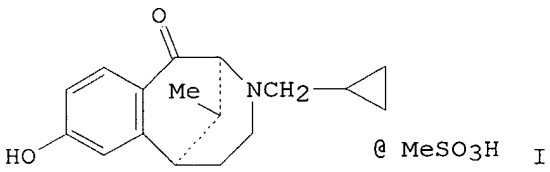
RN 11032-41-0 REGISTRY
CN Ergotoxine, dihydro- (8CI, 9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 8H-Oxazolo[3,2-a]pyrrolo[2,1-c]pyrazine, ergotoxine deriv.
CN Indolo[4,3-fg]quinoline, ergotoxine deriv.
OTHER NAMES:
CN 9,10-Dihydroergotoxine
CN Co-dergocrine
CN DCCK
CN DHETX
CN Dihydroergotoxin
CN **Dihydroergotoxine**
DR 52502-76-8
MF Unspecified
CI COM, MAN
LC STN Files: AGRICOLA, ANABSTR, BIOBUSINESS, BIOSIS, CA, CANCERLIT, CAPLUS, CBNB, CHEMCATS, CIN, CSCHEM, DDFU, DRUGU, EMBASE, IFICDB, IFIPAT, IFIUDB, IPA, MEDLINE, NAPRALERT, PHAR, PROMT, RTECS*, TOXLINE, TOXLIT, USAN, USPATFULL
(*File contains numerically searchable property data)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
277 REFERENCES IN FILE CA (1967 TO DATE)
6 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
277 REFERENCES IN FILE CAPLUS (1967 TO DATE)

AN 94:41512 CA
TI Ketazocine anesthetic method of use
IN Farah, Alfred E.
PA Sterling Drug, Inc., USA
SO U.S., 20 pp.
CODEN: USXXAM
DT Patent
LA English
FAN.CNT 1

| | PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|---|
| PI | US 4217354 | A | 19800812 | US 1979-11107 | 19790212 |
| | US 4294840 | A | 19811013 | US 1979-71774 | 19790831 |
| | JP 55120567 | A2 | 19800917 | JP 1980-14244 | 19800207 |
| PRAI | US 1979-11107 | 19790212 | | | |

GI




@ $MeSO_3H$ I

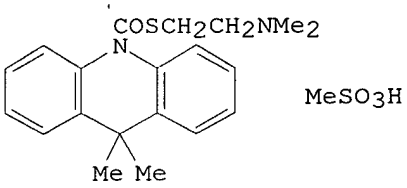
AB In dogs and monkeys, l-ketazocine **methane sulfonate** (l-I) [71697-06-8] produced good anesthesia. Premedication with diazepam [439-14-5] reversed the rigidity, tremors, and body jerks produced by I. Other side effects of I are described. Thus, **pharmaceutically** acceptable **salts** of racemic-I [58640-83-8] and l-I are good anesthetics in humans.

AN 71:105221 CA
TI Ajmalicine hydrochloride compositions for treating peripheral circulatory disorders
PA SIPHAR A. A.
SO Fr. M., 3 pp.
CODEN: FMXXAJ
DT Patent
LA French
FAN.CNT 1

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| FR 5078 | | 19670619 | FR | 19651115 |

AB A tablet compn. with very low toxicity for treating circulatory disorders was prepd. contg. ajmalicine-HCl (I) 4, dihydroergocristine methanesulfonate, m. 210.degree., 0.5, starch 110, lactone 75, and Mg stearate 10 g. I has [.alpha.]20D - 16 .+-. 2.degree. and LD50 165 mg./kg. (mouse), >200 mg./kg. (rat) (i.p.).

AN 87:15647 CA
TI Pharmacokinetics, enterohepatic circulation and biotransformation of [2-3H]-9,9-dimethylacridane-10-carboxylic acid S-(2-dimethylamino)thiolethyl ester in the rat and dog
AU Farrier, D. S.
CS Drug Res. Lab., Siegfried Ltd., Zofingen, Switz.
SO Arzneim.-Forsch. (1977), 27(3), 575-83
CODEN: ARZNAD
DT Journal
LA English
GI




I

AB Dogs receiving a 7.5 mg/kg oral or i.v. dose of 3H labeled 9,9-dimethylacridane-10-carboxylic acid S-(2-dimethylamino)thiolethyl ester methane **sulfonate** salt (DMA-MS)(I) [38044-69-8] excreted 86-95% of the radioactivity within 6 days. A similar recovery was obtained for rats receiving 300 mg/kg orally or 15 mg/kg i.v. In both species, approx. 66% of the dose was excreted in the feces as metabolites.

**Absorption** of the oral dose was 80% and 100% for the rat and dog, resp. Up to 47% of an i.v. dose was excreted in the bile of rats and an efficient enerohepatic circulation process insued. The parent **drug** was rapidly metabolized in the tissues yielding at least 6 polar metabolites which contributed to relatively long plasma half-lives in the order of 40 h for dogs and 58-90 h for rats. An atypical **increase** in plasma radioactivity following an i.v. dose could be rationalized in view of these results. Metabolite profiles were examined in plasma, urine, bile and feces and found to be qual. similar. Des-methyl-DMA [62868-65-9] and DMA-N-oxide [62868-64-8] were identified as two minor metabolites.

AN 109:803 CA
TI Choline sulfonate-containing absorption improvers for oral pharmaceuticals
IN Kitani. Tetsunori; Ikeda, Yasushi; Takakura, Isamu; Ohashi, Osamu; Motomura, Keiko; Yasuda, Takashi; Takamichi, Akira; Saikawa, Isamu
PA Toyama Chemical Co., Ltd., Japan
SO Jpn. Kokai Tokkyo Koho, 4 pp.
CODEN: JKXXAF
DT Patent
LA Japanese
FAN.CNT 1

| | PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|---|
| PI | JP 62226929 | A2 | 19871005 | JP 1986-69788 | 19860329 |
| | JP 06086392 | B4 | 19941102 | | |

AB The title absorption enhancers contain [R1HC(R2CO2)CO2(CH2)2NMe3+]n X- (I; R1, R2 = C1-5 lower alkyl; X = sulfonate; n = 1-4). A suspension of bacampicillin (10 mg/kg) in 0.5% CMC Na salt and an aq. soln. contg. I (R1 = R2 = Me, X = naphthalene-1,5-disulfonate, n = 2) (II) (1 mg/kg) were orally administered to mice. Bacampicillin was recovered 62% in urine, 47.6% in the controls given I without II. A capsule contg. II 50, corn starch 225, and a diluent 25 mg was prepd.

(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: 0 266 574 A2

# (12) EUROPEAN PATENT APPLICATION

(21) Application number: 87114648.6

(22) Date of filing: 07.10.87

(51) Int. Cl.⁴: C07D 211/22 , C07D 405/12 , A61K 31/445

(30) Priority: 03.11.86 DK 5232/86
25.06.87 DK 3234/87

(43) Date of publication of application:
11.05.88 Bulletin 88/19

(84) Designated Contracting States:
AT BE CH DE ES FR GB GR IT LI LU NL SE

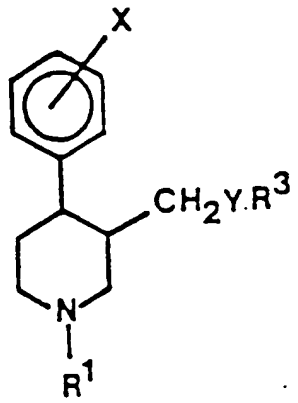
(71) Applicant: A/S FERROSAN
Sydmarken 5
DK-2860 Soeborg(DK)

(72) Inventor: Drejer, Jorgen
Klintevej 44
DK-2700 Bronshoj(DK)
Inventor: Jakobsen, Palle
Langkaer Vaenge 14
DK-3500 Vaerlose(DK)

(74) Representative: Patentanwälte Grünecker, Kinkeldey, Stockmair & Partner
Maximilianstrasse 58
D-8000 München 22(DE)

## (54) Piperidine compounds and their preparation and use.

(57) Novel piperidine compounds having the formula




wherein

R³ is 3,4-methylenedioxyphenyl, aryl or heteroaryl which are optionally substituted with one or more $C_{1-6}$-alkyl, $C_{1-6}$-alkoxy group, $C_{3-8}$-cycloalkyl, $C_{3-5}$-alkylene or aralkoxy,

R¹ is strait or branched $C_{4-8}$-alkyl, $C_{1-8}$-alkoxy-$C_{4-8}$-alkyl, $C_{4-7}$-cycloalkyl, aryloxy-$C_{3-8}$-alkyl, $C_{4-8}$-alkenyl, or $C_{\ldots}$-cycloalkylalkyl, or R1 may also be hydrogen or $C_{\ldots}$-alkyl, R1 is ... substituted with

EP 0 266 574 A2

# Piperidine Compounds and Their Preparation and Use

The present invention relates to therapeutically active piperidine compounds, a method of preparing the same and to pharmaceutical compositions comprising the compounds. The novel compounds are useful in the treatment of anoxia, ischemia, migraine and epilepsy.

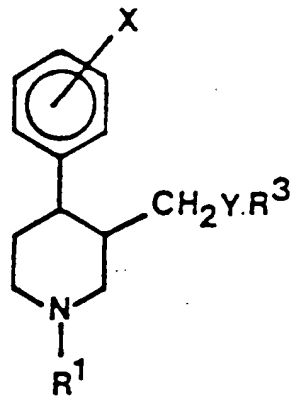
It is well known that accumulation of calcium in the brain cells (calcium overload) is seen after periods of uncontrolled hyperactivity in the brain, such as after convulsions, migraine, anoxia and ischemia. As the concentration of calcium in the cells is of vital importance for the regulation of cell function, an uncontrolled high concentration of the cell calcium will lead to, or indirectly cause the symptoms and possibly also the degenerative changes combined with the above diseases.

Therefore calcium overload blockers selective for brain cells will be useful in the treatment of anoxia, ischemia, migraine and epilepsy.

Well known calcium antagonists such as nifedipine, verapamil and diltiazem have activity against pheripheral calcium uptake, e.g. in blood vessels and the heart, however have shown only very low activity against calcium overload in brain cells.

Accordingly it is an object of the invention to provide novel compounds having activity against calcium overload in brain cells.

The novel compounds of the invention are piperidine compounds having the general formula I.




(I)

wherein

$R^3$ is 3,4-methylenedioxyphenyl, aryl or heteroaryl which are optionally substituted with one or more $C_{1-6}$-alkyl, $C_{1-6}$-alkoxy group, $C_{3-8}$-cycloalkyl, $C_{3-5}$-alkylene or aralkoxy,

$R^1$ is strait or branched $C_{4-8}$-alkyl, $C_{1-8}$-alkoxy-$C_{4-8}$-alkyl, $C_{4-7}$-cycloalkyl, aryloxy-$C_{3-8}$-alkyl, $C_{4-8}$-alkenyl, or $C_{4-8}$-cycloalkylalkyl, or $R^1$ may also be hydrogen or $C_{1-3}$ -alkyl, when $R^3$ is aryl, which is substituted with two or more of $C_{1-6}$-alkyl, $C_{1-6}$-alkoxy, $C_{3-8}$-cycloalkyl, aralkoxy, or with $C_{3-5}$-alkylene.

X is hydrogen or halogen, and wherein

Y is O or S

and a salt thereof with a pharmaceutically acceptable acid.

Examples of such salts include inorganic and organic acid addition salts such as hydrochloride, hydrobromide, sulphate, phosphate, acetate, fumarate, maleate, citrate, lactate, tartrate, oxalate, or similar pharmaceutically-acceptable inorganic or organic acid addition salts.

The invention also relates to a method of preparing the above mentioned compounds. This methods comprises

a) reacting a compound having the general formula II

Aliquots (0.050 ml) of this crude synaptosomal suspension are added to glass tubes containing 0.625 ml of NaCl buffer (136 mM NaCl, 4 mM KCl, 0.35 mM $CaCl_2$, 1.2 mM $MgCl_2$, 20 mM Tris HCl, 12 mM glucose, pH 7.4) and 0.025 ml of various drug solutions in 48% Ethanol. The tubes are pre-incubated for 30 min on ice and then for 6 min at 37°C in a water bath.

The uptake is immediately initiated by adding 0.4 ml of $^{45}CaCl_2$ (special activity = 29-39 Ci/g; 0.5 Ci/assay), in 145 mM NaCl for non-depolarized samples and in 145 mM KCl for depolarized samples. The incubation is continued for 15 s.

The uptake is terminated by rapid filtration through GF-C glass fiber filters which are washed three times with 5 ml of a cold solution containing 145 mM KCl, 7 mM EGTA and 20 mM Tris HCl, pH 7.4. The amount of radioactivity on the filter disc is determined by liquid scintillation spectrometry.

## TEST PROCEDURE

Test substances are dissolved in 10 ml of 48% ethanol at a concentration of 0.44 mg/ml. Dilution are made in 48% ethanol to give final concentrations of 0.1, 0.3, 1, 3 and 10 µg/ml. Experiments are performed in duplicate. Controls for depolarized and nondepolarized samples are included in the assay and test substances are only tested in depolarized samples. 25-75% inhibition of stimulated uptake must be obtained before calculating the $IC_{50}$ value.

## RESULTS

The test value will be given as $IC_{50}$ (the concentration (µg/ml) of test substance which inhibit 50% of stimulated uptake of $^{45}Ca$ (uptake in depolarized samples corrected for basal uptake in nondepolarized samples )). The $IC_{50}$ value is estimated from dose response curves.

Test results obtained by testing some compounds of the present invention will appear from the following table 1.

The compound of the invention, together with a conventional adjuvant, carrier, or diluent, and if desired in the form of a pharmaceutically-acceptable acid addition salt thereof, may be placed into the form of pharmaceutical compositions and unit dosages thereof, and in such form may be employed as solids, such as tablets of filled capsules, or liquids, such as solutions, suspensions, emulsions, elixirs, or capsules filled with the same, all for oral use, in the form of suppositories for rectal administration; or in the form of sterile injectable solutions for parenteral (including subcutaneous) use. Such pharmaceutical compositions and unit dosage forms thereof may comprise conventional ingredients in conventional proportions, with or without additional active compounds or principles, and such unit dosage forms may contain any suitable effective calcium overload blocking amount of the active ingredient commensurate with the intended daily dosage range to be employed. Tablets containing ten (10) milligrams of active ingredient or, more broadly, ten (10) to hundred (100) milligrams, per tablet, are accordingly suitable representative unit dosage forms.

The compounds of this invention can thus be used for the formulation of pharmaceutical preparations, e.g. for oral and parenteral administration to mammals including humans, in accordance with conventional methods of galenic pharmacy.

Conventional excipients are such pharmaceutically acceptable organic or inorganic carrier substances suitable for parenteral or enteral application which do not deleteriously react with the active compounds.

Examples of such carriers are water, salt solutions, alcohols, polyethylene glycols, polyhydroxyethoxylated castor oil, gelatine, lactose, amylose, magnesium stearate, talc, silicic acid, fatty acid monoglycerides and diglycerides, pentaerythritol fatty acid esters, hydroxymethylcellulose and polyvinylpyrrolidone.

The pharmaceutical preparations can be sterilized and mixed, if desired, with auxiliary agents, emulsifiers, salt for influencing osmotic pressure, buffers and/or coloring substances and the like, which do not deleteriously react with the active compounds.

For parenteral application, particularly suitable are injectable solutions or suspensions, preferably aqueous solutions with the active compound dissolved in polyhydroxylated castor oil.

Ampoules are convenient unit dosage forms.

Tablets,dragees, or capsules having talc and/or a carbohydrate carrier or binder or the like, the carrier preferably being lactose and/or corn starch and/or potato starch, are particularly suitable for oral application. A syrup, elizir of the like can be used in cases where a sweetened vehicle can be employed.

Generally, the compounds of this invention are dispensed in unit form comprising 0.05-100 mg in a pharmaceutically acceptable carrier per unit dosage.

The dosage of the compounds according to this invention is 0.1-300 mg/day, preferably 10-100 mg/day, when administered to patients, e.g. humans, as a drug.

A typical tablet which may be prepared by conventional tabletting techniques contains:

| | |
|---|---|
| Active compound | 5.0 mg |
| Lactosum | 67.8 mg Ph.Eur. |
| Avicel™ | 31.4 mg |
| Amberlite™IRP 88 | 1.0 mg |
| Magnesii stearas | 0.25 mg Ph.Eur. |

Due to the high calcium overload blocking activity , the compounds of the invention are extremely useful in the treatment symptoms related to an accumulation of calcium in brain cells of mammals , when administered in an amount effective for blocking calcium overload in brain cells . The important calcium overload blocking activity of compounds of the invention includes both activity against anoxia, ischemia, migraine and epilepsy . The compounds of the invention may accordingly be administered to a subject, e.g., a living animal body, including a human, in need of a calcium overload blocker , and if desired in the form of a pharmaceutically-acceptable acid addition salt thereof (such as the hydrobromide, hydrochloride, or sulfate, in any event prepared in the usual or conventional manner, e.g., evaporation to dryness of the free base in solution together with the acid), ordinarily concurrently, simultaneously, or together with a pharmaceutically-acceptable carrier or diluent, especially and preferably in the form of a pharmaceutical composition thereof, whether by oral, rectal, or parenteral (including subcutaneous) route, in an effective calcium overload blocking amount, and in any event an amount which is effective for the treatment of anoxia, ischemia, migraine or epilepsy due to their calcium overload blocking activity. Suitable dosage ranges are 1-200 milligrams daily, 10-100 milligrams daily, and especially 30-70 milligrams daily, depending as usual upon the exact mode of administration, form in which administered, the indication toward which the administration is directed, the subject involved and the body weight of the subject involved, and the preference and experience of the physician or veterinarian in charge.

The invention will now be described in further detail with reference to the following

dissolution in acetone and precipitation by addition of diethyl ether.
** 1-Butanol was used as solvent instead of ethanol.

(-)-trans-4-(-4-fluorophenyl)-3-(3,4-methylenedioxyphenoxymethyl)-1-(2-ethoxyethyl)-piperidine hydrochloride as an glass M.p. 49.5°C by refluxing the reaction mixture for 6 hours.

(-)-trans-4-(-4-fluorophenyl)-3-(3,4-methylenedioxyphenoxymethyl)-1-(2-methoxymethyl)-piperidine hydrochloride M.p. 164.7°C by refluxing the reaction mixture for 48 hours.

(-)-trans-4-(-4-fluorophenyl)-3-(3,4-methylenedioxyphenoxymethyl)-1-(2-trans-butenyl)-piperidine hydrochloride M.p. 195.5°C by refluxing the reaction mixture for 3 hours.

(-)-trans-4-(-4-fluorophenyl)-3-(3,4-methylenedioxyphenoxymethyl)-1-(3-butenyl)-piperidine hydrochloride M.p. 198.6°C by refluxing the reaction mixture for 288 hours.

(-)-trans-4-(-4-fluorophenyl)-3-(3,4-methylenedioxyphenoxymethyl)-1-(5-hexenyl)-piperidine hydrochloride M.p. 123.1°C by refluxing the reaction mixture for 3 hours.

(-)-trans-4-(-4-fluorophenyl)-3-(3,4-methylenedioxyphenoxymethyl)-1-(4-pentenyl)-piperidine hydrochloride M.p. 177.7°C by refluxing the reaction mixture for 3 hours.

(-)-trans-4-(-4-fluorophenyl)-3-(3,4-methylenedioxyphenoxymethyl)-1-(3-methyl-butenyl)-piperidine hydrochloride M.p. 239.2°C by refluxing the reaction mixture for 4.5 hours.

(-)-cis-4-(-4-fluorophenyl)-3-(3,4-methylenedioxyphenoxymethyl)-1-pentylpiperidine hydrochloride M.p. 195.3°C and (+)-cis-4-(-4-fluorophenyl)-3-(3,4-methylenedioxyphenoxymethyl)-1-pentylpiperidine hydrochloride M.p. 193.7°C were prepared exactly as described above from pentyl bromide, and (-)-cis-4-(-4-fluorophenyl)-3-(3,4-methylenedioxyphenoxymethyl)-piperidine hydrochloride and (+)-cis-4-(-4-fluorophenyl)-3-(3,4-methylendioxyphenoxymethyl)-piperidine hydrochloride respectively.

Example 2

(-)-trans-1-butyl-4-(4-fluorophenyl)-3-(4-methoxyphenoxymethyl)-piperidine hydrochloride

(-)-trans-1-butyl-4-(4-fluorophenyl)-3-(4-methoxyphenoxymethyl)-piperidine hydrochloride M.p. 163-165°C was prepared exactly as described in example 1 from (-)-trans-4-(4-fluorophenyl)-3-(4-methoxyphenoxymethyl)-piperidine hydrochloride and butyl bromide by refluxing for 120 hours.

The following compounds were prepared in exactly the same manner from (-)-trans-4-(4-fluorophenyl)-3-(4-methoxyphenoxymethyl)-piperidine hydrochloride and the corresponding alkyl bromide or cycloalkyl bromide.

(-)-trans-1-propyl-4-(4-fluorophenyl)-3-(4-methoxyphenoxymethyl)-piperidine hydrochloride M.p. 196-197°C by refluxing the reaction mixture for 7 hours.

(-)-trans-1-ethyl-4-(4-fluorophenyl)-3-(4-methoxyphenoxymethyl)-piperidine hydrochloride M.p. 190-191°C by refluxing the reaction mixture for 170 hours.

(-)-trans-1-isopropyl-4-(4-fluorophenyl)-3-(4-methoxyphenoxymethyl)-piperidine hydrochloride as an oil by refluxing the reaction mixture for 210 hours.

(-)-trans-1-(2-(4-methoxyphenoxyethyl))-4-(4-fluorophenyl)-3-(4-methoxyphenoxymethyl)-piperidine hydrochloride as an oil by refluxing the reaction mixture for 48 hours.

(-)-trans-1-pentyl-4-(4-fluorophenyl)-3-(4-methoxyphenoxymethyl)-piperidine hydrochloride as a glass M.p. 53.5°C by refluxing the reaction mixture for 8 hours.

(-)-trans-1-heptyl-4-(4-fluorophenyl)-3-(4-methoxyphenoxymethyl)-piperidine hydrochloride M.p. 138.1°C by refluxing the reaction mixture for 8 hours.

(-)-trans-1-cyclohexyl-4-(4-fluorophenyl)-3-(4-methoxyphenoxymethyl)-piperidine hydrochloride M.p. 220.3°C by refluxing the reaction mixture for 330 hours.**
** 1-Butanol was used as solvent instead of ethanol.

Example 3

(+) trans 3-(3,4-Methylenedioxyphenoxymethyl)-1-pentyl-4-phenylpiperidine, HCl. m.p. 175.0°C. Reaction time 2.5h.

(+-) trans 3-(4-Benzyloxyphenoxymethyl)-1-pentyl-4-phenylpiperidine, HCl. m.p. 139.5°C. Reaction time 17h.

(+-) trans 1-Allyl-3-(4-benzyloxyphenoxymethyl)-4-phenylpiperidine, HCl. m.p. 212.1°C. Reaction time 3.5h. Equimolar amounts of piperidine-compound and allyl bromide was used.

(-) trans 3-(4-Methoxyphenoxymethyl)-1-pentyl-4-phenylpiperidine, HCl. m.p. 138.7°C. Reaction time 18h.

(-) trans 1-Allyl-3-(4-methoxyphenoxymethyl)-4-phenylpiperidine, HCl. m.p. 197.5°C. Reaction time 1.5h. Equimolar amounts of allyl bromide and piperidine-compound was used.

(+) trans 3-(4-Methoxyphenoxymethyl)-1-pentyl-4-phenylpiperidine, HCl. m.p. 138.7°C. Reaction time 18.5h.

(+) trans 1-Allyl-3-(4-methoxyphenoxymethyl)-4-phenylpiperidine, HCl. m.p. 195.°C. Reaction time 20.5h. Equimolar amounts of allyl bromide and piperidine-compound was used.

(-) trans 4-(4-Fluorophenyl)-1-pentyl-3-(5,6,7,8-tetrahydro-2-naphthoxymethyl)-piperidine, HCl. m.p. 55.3°C (hard glass). Reaction time 2h. The crude product was purified on a silicagel column, $CHCl_3/CH_3OH$ (9/1) as eluent.

(-) trans 3-(2-Benzothiazolylthiomethyl)-4-(4-fluorophenyl)-1-pentylpiperidine, HCl. m.p. 199.9°C. Reaction time 7h.

(-) trans 4-(-Fluorophenyl)-3-(2-naphthoxymethyl)-1-pentylpiperidine, HCl. m.p. 54.6°C (hard glass). Reaction time 4.5h. The crude product was purified on a silicagel column with $CHCl_3/CH_3OH$ (9/1) as eluent.

(-) trans 1-Butyl-4-(4-fluorophenyl)-3-(5,6,7,8-tetrahydro-2-naphthoxymethyl)-piperidine, HCl. M.p. 154.3°C. Reaction time 2.5 h.

(-) trans 4-(4-Fluorophenyl)-1-propyl-3-(5,6,7,8-tetrahydro-2-naphthoxymethyl)-piperidine, HCl. M.p. 186.6°C. Reaction time 3.5 h.

(-) trans 4-(4-Fluorophenyl)-1-hexyl-3-(5,6,7,8-tetrahydro-2-naphthoxymethyl)-piperidine, HCl. M.p. 146.7°C. Reaction time 4 h. The crude product was purified on a silicagel column with $CHCl_3/CH_3OH$ (9/1) as eluent.

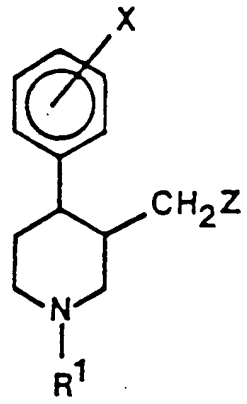
(-) trans 1-Ethyl-4-(4-Fluorophenyl)-3-(5,6,7,8-tetrahydro-2-naphthoxymethyl)-piperidine, HCl. M.p. 217.0°C. Reaction time 24 h. The crude product was purified on a silicagel column with $CHCl_3/CH_3OH$ (9/1) as eluent.

Example 6

(-) trans 3-(2-Benzothiazolylthiomethyl)-4-(4-fluorophenyl)-1-methylpiperidine,HCl was prepared by refluxing a mixture of 5g benzothiazol-2-thiol, 7,1g (-) trans-(3-chloromethyl)-4-(4-fluoromethyl)-1-methylpiperidine and 5g potassium carbonate in ethanol for 24h. Acetone/ether was added, the mixture filtered and the filtrate evaporated to drynes. The residue was extracted from NaOH/ether, the ether layer dried with $K_2CO_3$, acidified with conc. HCl to pH2, and evaporated to dryness. The resulting oil was crystallized from acetone/ether. m.p. 204.2°C.

$R^1$-Z , wherein Z is a leaving group such as halogen and $R^1$ has the meaning defined above,

b) reacting a compound having the general formula III



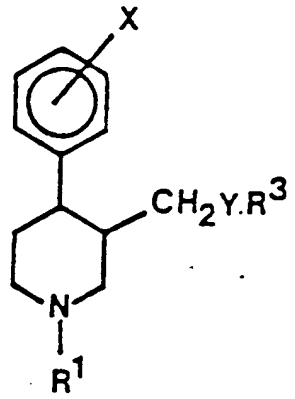
(III)

wherein $R^1$ and X have the meanings defined above, and Z is a leaving group, with a compound having the the general formula $R^3$-YH, wherein Y is O or S and $R^3$ has the meaning defined above.

7. A pharmaceutical composition suitable for use in preventing calcium overload in brain cells of mammals, including humans, comprising an amount of a compound of claim 1, or which is effective for inhibiting calcium uptake into brain cells together with a pharmaceutically-acceptable carrier or diluent.

8. A pharmaceutical composition according to claim 7 wherein it is in the form of an oral dosage unit containing 1-100 mg of the active compound.

9. The use of a compound having the formula IV



(IV)

wherein

$R^3$ is 3,4-methylenedioxyphenyl, aryl or heteroaryl which are optionally substituted with one or more $C_{1-6}$-alkyl, $C_{1-6}$-alkoxy group, $C_{3-8}$-cycloalkyl, $C_{3-5}$-alkylene or aralkoxy,

$R^1$ is hydrogen or strait or branched $C_{1-8}$-alkyl, $C_{1-8}$-alkoxy-$C_{1-8}$-alkyl, $C_{1-7}$-cycloalkyl, aryloxy-$C_{1-8}$-alkyl, $C_{1-8}$-alkenyl, or $C_{1-8}$ -cycloalkylalkyl,

X is hydrogen or halogen, and wherein

Y is O or S

and a salt thereof with a pharmaceutically acceptable acid

for the preparation of a medicament useful in the treatment of calcium overload in brain cells of mammals, including humans.

US005955475A

# United States Patent [19]

Krape et al.

[11] Patent Number: 5,955,475

[45] Date of Patent: Sep. 21, 1999

[54] **PROCESS FOR MANUFACTURING PAROXETINE SOLID DISPERSIONS**

[75] Inventors: **Philip J. Krape**, Wilmington, Del.; **Sou-Chan Chang**, Westbury, N.Y.; **William A. Hein, II**, Hasbrouck Heights, N.J.; **Christopher A. Teleha**, Bear, Del.

[73] Assignee: **Endo Pharmaceuticals Inc.**, Chadds Ford, Pa.

[21] Appl. No.: **08/885,068**

[22] Filed: **Jun. 30, 1997**

[51] **Int. Cl.**[6] ..... **A61K 31/445**

[52] **U.S. Cl.** ..... **514/321**; 514/937

[58] **Field of Search** ..... 514/321

[56] **References Cited**

U.S. PATENT DOCUMENTS

| | | | |
|---|---|---|---|
| 4,007,146 | 2/1977 | Christuensen et al. | 260/293.58 |
| 4,721,723 | 1/1988 | Barnes et al. | 514/321 |
| 4,933,360 | 6/1990 | Pandit et al. | 514/417 |

FOREIGN PATENT DOCUMENTS

| | | |
|---|---|---|
| WO 9515155 A1 | 6/1995 | WIPO . |
| WO 9516448 A1 | 6/1995 | WIPO . |
| WO 9631197 A1 | 10/1996 | WIPO . |

*Primary Examiner*—Leonard Schenkman

*Attorney, Agent, or Firm*—Schnader Harrison Segal & Lewis LLP; Michael B. Fein

[57] **ABSTRACT**

Solid dispersions of poorly soluble drugs are disclosed which are prepared using a solvent or fusion process. Such dispersions are manufactured with the free base of the drug, specifically paroxetine free base, an oil, allowing for a low temperature for the fusion process, decreased organic solvent volumes for the solvent process and the formation of a paroxetine salt during the solid dispersion manufacture process.

**27 Claims, No Drawings**

# PROCESS FOR MANUFACTURING PAROXETINE SOLID DISPERSIONS

## FIELD OF THE INVENTION

The present invention relates to the field of solid dispersions of poorly water soluble drugs, to processes for their preparation and their use in pharmaceutical compositions. Specifically, the present invention relates to solid dispersions resulting from fusion or solvent methods for the incorporation of poorly water soluble drugs into pharmaceutically acceptable carriers. More specifically, the invention relates to the solid dispersions of paroxetine, processes for the preparation of such solid dispersions, pharmaceutical compositions containing the same and their use thereof in therapy.

## BACKGROUND

The compound (−)-trans-4-((4'-fluorophenyl)3-(3'4'-methylenedioxyphenoxymethyl)-piperidine, commonly known as paroxetine, is a viscous oil and poorly water soluble drug with a commercial need for useful pharmaceutical compositions. A solid dispersion of paroxetine or its acid addition salt, never described before now in the literature, would provide a solid product on a commercial scale with good handling qualities and physiological acceptability without the need or expense to manufacture crystalline materials.

Pharmaceutical compositions with good dissolution and bioavailability can be formulated from solid dispersions of pharmaceutically active ingredients. Advantages claimed for pharmaceutical solid dispersions include potential use in controlled release formulations, stabilizing the drug from polymorphic conversions, improving poor handling properties of drug substances and protecting certain drugs against decomposition during administration. Solid dispersions of pharmaceutically active ingredients can be formed from a number of pharmaceutically acceptable carriers. U.S. Pat. No. 4,933,360 describes a novel process and product comprising chlorthalidone as the pharmaceutical active ingredient and polyvinylpyrrolidone (PVP) as the pharmaceutically acceptable carrier. The techniques have been described in general by W. L. Chiou et al., J. Pharm. Sci. 60(28)(1971) and S. Riegelman et al, U.S. Pat. No. 4,151,273. As defined in the Chiou article the term "solid state dispersion" means a dispersion of one or more active ingredients in an inert carrier or matrix in a solid state prepared by a melting (fusion), solvent, or combined melt-solvent method. The dispersion of an active ingredient in a solid carrier or diluent by traditional mechanical mixing is not included within the definition of this term.

In the "solvent method", the active ingredient is conventionally dispersed in a water soluble carrier by dissolving a physical mixture containing the active ingredient and the pharmaceutically acceptable carrier in a common organic solvent and then removing the solvent by evaporation. The resulting solid dispersion is recovered and used in the preparation of suitable pharmaceutical compositions formulated using conventional methods.

Manufacture of solid dispersions by the fusion or "melt" process involves combination of the pharmaceutically acceptable carrier and the poorly water soluble drug where the two components are allowed to melt at temperatures at or above the melting point of both the drug and the carrier. In the fusion process, the drug and carrier are first physically mixed and then both are melted. The molten mixture is then cooled rapidly to provide a congealed mass which is subsequently milled to produce a powder. Spray-congealing techniques used to produce pellets have been described by Kanig (J. Pharm. Sci. 53, 188 (1964)) for dispersions containing mannitol and by Kreuschner et al. (Acta Pharm. Tech. 26, 159 (1980)) for phenylbutazone-urea.



In general, problems which can be associated with known melting (fusion), solvent, melt solvent, and coprecipitation techniques can include excess solvent usage, identifying carrier/drug combinations that can be conveniently melted (fused) or codissolved, the use of heat to effect solution or fusion which may result in decomposition of the drug and/or carrier, and identifying conditions and properties effecting coprecipitation. Salts of drugs may present particular problems with identifying organic solvents or solvents capable of dissolving both the drug and a pharmaceutically acceptable carrier.

U.S. Pat. No. 4,007,196 discloses paroxetine as an inhibitor of 5-hydroxytryptamine (5HT) uptake and thus of therapeutic use as an anti-depressant. Paroxetine is well known and widely marketed as a medicinal agent. As disclosed in U.S. Pat. No. 4,007,196, paroxetine is obtained as the free base and then converted to its maleate salt. However, paroxetine is a poorly water soluble drug and difficult to formulate into useful pharmaceutical compositions.

U.S. Pat. No. 4,721,723 indicates that because of its basicity, it is preferred that paroxetine be used as a therapeutic agent in the form of an acid addition salt. The free base is a viscous oil which is difficult to handle and formulate into a finished dosage form for therapeutic use. As such, U.S. Pat. No. 4,721,723 further discloses crystalline paroxetine hydrochloride hemihydrate as a novel material with better handling properties than anhydrous paroxetine hydrochloride which is an hygroscopic solid with poor handling properties.

In general, the hydrochloride salt of a basic compound is preferred for therapeutic use because of its physiological acceptability. Additionally, a pharmaceutically active ingredient should not contain appreciable amounts of bound or unbound organic solvent. Once the salt has been formed, it must be isolated from solvents by filtration or other means in order for the paroxetine salt to be conveniently formulated into a pharmaceutical composition. Many solvents, including water, form solvates or clathrates of paroxetine hydrochloride wherein the solvent cannot be removed by conventional drying techniques such as vacuum oven drying. U.S. Pat. No. 4,721,723 discloses the hemihydrate solvate form of paroxetine hydrochloride while International Publication Number WO 96/24595 discloses paroxetine hydrochloride solvates other than the propan-2-ol solvate as precursors in the preparation of paroxetine hydrochloride substantially free of bound organic solvent. Additionally, International Publication Number WO 96/24595 also discloses four novel paroxetine hydrochloride anhydrates substantially free of bound solvent. However, none of the above publications specifically describe the stability or hygroscopicity of non-crystalline anhydrates of paroxetine hydrochloride in a solid dispersion.

The present invention relates to novel processes for incorporating paroxetine, a poorly water soluble drug, into a solid dispersion and its use in pharmaceutical compositions containing the same.

It has now been surprisingly found that solid dispersions of anhydrous paroxetine hydrochloride can be manufactured by a fusion process using the free base of paroxetine, and dry hydrogen chloride gas at temperatures substantially lower then the melting point of paroxetine hydrochloride using a

pharmaceutically acceptable carrier with a melting point significantly lower than that of anhydrous paroxetine hydrochloride. The resulting solid dispersion is substantially free of organic solvent, is anhydrous and has improved handling properties.

Furthermore, it has been found that solid dispersions of anhydrous paroxetine salts, preferably the hydrochloric acid salt, can be manufactured by a novel solvent process using a pharmaceutically acceptable carrier, paroxetine free base, a non-aqueous solvent and a solution or gas of the acid addition salt.

The manufacturing of noncrystalline anhydrates of paroxetine hydrochloride in a solid dispersion improves the formulating of paroxetine free base, provides a solid which is readily formulated into a commercial dosage form, eliminates the additional steps to manufacture crystalline material for handling purposes and presumptively reduces manufacturing costs associated with those steps.

## SUMMARY OF THE INVENTION

Solid dispersions of poorly soluble drugs are disclosed which are prepared using a solvent or fusion process. Such dispersions are manufactured with the free base of the drug, specifically paroxetine free base, an oil, allowing for a low temperature for the fusion process, decreased organic solvent volumes for the solvent process and the formation of a paroxetine salt during the solid dispersion manufacture process.

## DETAILED DESCRIPTION OF THE INVENTION

In a first embodiment the invention provides a process for preparing a water soluble solid state dispersion of paroxetine and a pharmaceutically acceptable polymeric carrier, which process comprises:

(a) forming a solution of a water soluble pharmaceutically acceptable polymeric carrier and a non-aqueous solvent,

(b) dissolving paroxetine free base into the solution, wherein the ratio by weight of water soluble pharmaceutically acceptable polymeric carrier to paroxetine is in the range of about 4:1 to about 1:1;

(c) contacting the paroxetine free base in solution with at least one equivalent of an acid, wherein the acid is a non-toxic inorganic or organic acid, to form a pharmaceutically acceptable paroxetine salt in solution; and

(d) removing the non-aqueous solvent by evaporation under vacuum.

In a preferred embodiment the invention provides a process for preparing a water soluble solid state dispersion wherein the polymeric carrier is polyethylene glycol or polyvinylpyrrolidone.

In a more preferred embodiment the invention provides a process for preparing a water soluble solid state dispersion of paroxetine and a pharmaceutically acceptable polymeric carrier, which process comprises:

(a) forming a solution of polyethylene glycol and ethanol,

(b) dissolving paroxetine free base into the solution, wherein the ratio by weight of polyethylene glycol to paroxetine is in the range of about 4:1 to about 1:1;

(c) contacting the paroxetine free base in solution with at least one equivalent of dry hydrogen chloride, wherein the dry hydrogen chloride is dissolved in methanol or ethanol, to form pharmaceutically acceptable paroxetine hydrogen chloride in solution; and

(d) removing the non-aqueous solvent by evaporation under vacuum.

In an even more preferred embodiment the invention provides a process for preparing a water soluble solid state dispersion of paroxetine and a pharmaceutically acceptable polymeric carrier, which process comprises:

(a) forming a solution of polyvinylpyrrolidone and ethanol,

(b) dissolving paroxetine free base into the solution, wherein the ratio by weight of polyvinylpyrrolidone to paroxetine is in the range of about 4:1 to about 1:1;

(c) contacting the paroxetine free base in solution with at least one equivalent of dry hydrogen chloride, wherein the dry hydrogen chloride is dissolved in methanol or ethanol, to form pharmaceutically acceptable paroxetine hydrogen chloride in solution; and

(d) removing the non-aqueous solvent by evaporation under vacuum.

In a second embodiment the invention provides a process for preparing a water soluble solid state dispersion of paroxetine and a pharmaceutically acceptable polymeric carrier, which process comprises:

(a) contacting a water soluble pharmaceutically acceptable polymeric carrier with paroxetine free base to form an intimate mixture, wherein the ratio by weight of water soluble pharmaceutically acceptable polymeric carrier to paroxetine free base is in the range of about 4:1 to about 1:1 ;

(b) heating the mixture to form a molten homogeneous melt of polymeric carrier and paroxetine free base;

(c) contacting the molten homogeneous melt of polymeric carrier and paroxetine free base with at least one equivalent of dry hydrogen chloride to form pharmaceutically acceptable paroxetine hydrogen chloride in the molten homogeneous melt; and

(d) cooling the molten homogeneous melt to form a water soluble solid state dispersion.

In a preferred second embodiment the invention provides a process for preparing a water soluble solid state dispersion of paroxetine and a pharmaceutically acceptable polymeric carrier, which process comprises:

(a) contacting a polyethylene glycol with paroxetine free base to form an intimate mixture, wherein the ratio by weight of polyethylene glycol to paroxetine free base is in the range of about 4:1 to about 1:1;

(b) heating the mixture to form a molten homogeneous melt of polyethylene glycol and paroxetine free base;

(c) contacting the molten homogeneous melt of polyethylene glycol and paroxetine free base with at least one equivalent of dry hydrogen chloride to form pharmaceutically acceptable paroxetine hydrogen chloride in the molten homogeneous melt; and

(d) cooling the molten homogeneous melt to form a water soluble solid state dispersion.

In a third embodiment the invention provides a solid state dispersion comprising a pharmaceutically acceptable polymeric carrier and paroxetine.

In a fourth embodiment the invention provides for a pharmaceutical composition comprising one or more pharmaceutically acceptable excipients and a solid state dispersion comprising paroxetine and a pharmaceutically acceptable polymeric carrier.

In a fifth embodiment the invention provides for a method of treating depression in a warm-blooded animal comprising administering to said animal a solid state dispersion, com-

prising paroxetine and a pharmaceutically acceptable polymeric carrier, the amount of paroxetine hydrochloride in said dispersion being effective for treating depression.

By "paroxetine" it is meant the generic name for the compound described in Example 2 of U.S. Pat. No. 4,007,196, also known as (−)-trans-4-(4'-fluorophenyl)-3-(3',4'-methylenedioxyphenoxymethyl)-piperidine, and pharmaceutically acceptable salts thereof. Therefore, as used herein, the term paroxetine refers to "paroxetine free base" or "paroxetine salt". The term "paroxetine free base", or simply "free base", specifically refers to paroxetine as a material which is a viscous oil at standard temperature and pressure. The term "paroxetine salt" is used to describe an acid addition product of paroxetine. For example, in the case of the hydrogen chloride, the acid addition product is called "paroxetine hydrochloride" or simply "hydrochloride salt."

The compound paroxetine herein described has two asymmetric centers. Unless otherwise indicated, the (−)-trans isomer is the preferred enantiomer. However, all chiral, diastereomeric and racemic forms are included in the present invention. It is well known in the art how to prepare optically active forms, such as by resolution of racemic forms or by synthesis, from optically active starting materials. Use of all chiral, diastereomeric, racemic forms are intended, unless the specific stereochemistry or isomer form is specifically indicated.

As used herein, the term "non-aqueous solvent" refers to any of the following: methanol, ethanol, n-propanol, i-propanol, n-butanol, i-butanol, s-butanol, toluene, benzene, supercritical liquid $CO_2$, chloroform, methylene chloride, acetonitrile, ketones (for example, but not limited to, dimethylketone, methylethylketone, and diethylketone), dimethylformamide, dimethylsulfoxide, esters (for example, but not limited to, ethyl acetate), ethers (for example, but not limited to, diethylether and dipropylether), 1,4-dioxane, tetrahydrofuran, pentanes, hexanes, heptanes, trichloroethene, or suitable mixtures of thereof.

Preferably the solvent should be (a) capable of dissolving both the active ingredient and the carrier, (b) chemically inert with respect to the active ingredient and the carrier, and (c) sufficiently volatile to permit removal by evaporation using conventional techniques. Alkanols having from one to four carbon atoms would in general be expected to be useful for preparing solid state dispersions by the solvent method. In the present invention additional characteristics have been found to be important. The organic solvent should be (d) capable of dissolving both the free base and the pharmaceutically acceptable salt of the active ingredient; (e) chemically inert with respect to both the free base of the active ingredient and the salt formed after reaction with the acidified organic solvent; and (f) capable of dissolving sufficient acid to permit complete or nearly complete conversion of the free base to the salt.

As used herein, the term "pharmaceutically acceptable polymeric carrier", or "polymeric carrier" refers to any of the following: hydroxypropyl cellulose, methyl cellulose, carboxymethyl cellulose, sodium carboxymethyl cellulose, cellulose acetate phthalate, cellulose acetate butyrate, hydroxyethyl cellulose, ethyl cellulose, polyvinyl alcohol, polypropylene, dextrans, dextrins, hydroxypropyl-beta-cyclodextrin, chitosan, co(lactic/glycolid) copolymers, poly(orthoester), poly(anhydrate), polyvinyl chloride, polyvinyl acetate, ethylene vinyl acetate, lectins, carbopols, silicon elastomers, polyacrylic polymers, maltodextrins, lactose, fructose, inositol, trehalose, maltose, raffinose, polyvinylpyrrolidone (PVP), polyethylene glycol (PEG), and alpha-, beta-, and gamma-cyclodextrins, or suitable mixtures of thereof.

In the present invention, additional characteristics have been found to be important. The pharmaceutically acceptable carrier should be (a) capable of being miscible with both the free base and the salt form of the drug substance, (b) capable of keeping the salt in a homogeneous noncrystalline solid state dispersion after the solvent has been removed by evaporation and (c) chemically inert with respect to the free base of the active ingredient, the salt of the free base, and the acidified organic solvent.

As used herein, the term "pharmaceutically acceptable salt" refers to derivatives of paroxetine wherein paroxetine is modified by making acid addition salts of the compound. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of the basic piperidine residue; and the like. The pharmaceutically acceptable salts of paroxetine include conventional non-toxic salts or quaternary ammonium salts, for example, from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric and the like; and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pamoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethanesulfonic, ethanedisulfonic, oxalic, isethionic, and the like.

The pharmaceutically acceptable salts of paroxetine can be prepared according to the method of the present invention would include introduction of or delivery of the acid moiety by various means. In the fusion method, the acidic moiety would be introduced in neat form. In the solution method, the acidic moiety could be introduced in neat form or by the non-aqueous solvent, which is later removed. Generally, the salts are prepared by reacting the free base with stoichiometric amounts or with an excess of the desired salt-forming inorganic or organic acid.

Lists of suitable salts are found in *Remington's Pharmaceutical Sciences,* 17th ed., Mack Publishing Company, Easton, PA, 1985, p. 1418, the disclosure of which is hereby incorporated by reference.

As used herein, the term "dry hydrogen chloride gas" refers to hydrogen chloride gas commercially available in cylinders containing compressed gas which is dried before use. Generally, dry hydrogen chloride gas is commercially prepared by bubbling hydrogen chloride gas through concentrated sulfuric acid or a comparable drying agent.

The disclosure of all references used herein are hereby incorporated by reference.

It is the object of the present invention to provide improved processes for the preparation of a water soluble solid dispersion of a poorly water soluble drug or drug combination prepared by a fusion and/or solvent process for producing solid dispersions. The methods of the present invention, by way of example, and without limitation, may be further understood by the following descriptive procedures.

The general method for preparation of a solid dispersion by the solvent process proceeds by (1) forming a solution comprising a pharmaceutically acceptable carrier and a non-aqueous solvent. A preferred polymeric carrier is selected from one or more of polyvinylpyrrolidone, hydroxypropylmethyl cellulose, hydroxypropyl cellulose, methyl cellulose, block co-polymers of ethylene oxide and propylene oxide, and polyethylene glycol, wherein a more preferred polymeric carrier is either polyethylene glycol (PEG) having an average molecular weight of from about 1,000 to

about 20,000 or polyvinylpyrrolidone (PVP) having an average molecular weight of from about 2,500 to about 3,000,000. A most preferred polymeric carrier is polyvinylpyrrolidone having an average molecular weight of from about 10,000 to about 450,000. A preferred non-aqueous solvent is an alcohol selected from methanol, ethanol, n-propanol, iso-propanol, n-butanol, iso-butanol, and sec-butanol, wherein a more preferred solvent is either methanol or ethanol, wherein a most preferred solvent is ethanol. It is also preferred that the non-aqueous solvent be dry or anhydrous. In forming a solution of a polymeric carrier and a non-aqueous solvent it is understood that heating of the solution is allowable, but is not required, provided that the temperature does not result in decomposition or degradation of any materials.

Upon forming said solution the process proceeds by (2) dissolving the free base of a poorly water soluble drug in the solution thus formed. Heating is allowable as in step (1) but not required. It is understood that the addition of a poorly soluble drug is not limited to one drug but might encompass a combination of one or more drugs provided at least one drug is a poorly water soluble drug in the form of a free base. It is preferred that the poorly water soluble drug in the form of a free base is paroxetine. The ratio by weight of water soluble pharmaceutically acceptable polymeric carrier to paroxetine is in the range of about 5:1 to about 1:1; preferably about 4:1 to about 1:1; more preferably about 3:1 to about 1.5:1; most preferably about 2:1.

It is also understood that the order of addition for the polymeric carrier, the nonaqueous solvent and the free base of the poorly water soluble drug is interchangeable. For example, the free base drug could be dissolved into the non-aqueous solvent after which the polymeric carrier is added.

Upon dissolution of the free base drug the process proceeds by (3) converting the free base to a pharmaceutically acceptable preferably the free base salt, preferably the paroxetine salt, can be formed by addition of an inorganic or an organic acid which preferably is non-toxic and pharmaceutically acceptable. The acid is added either as a gas, a liquid or as a solid dissolved into a nonaqueous solvent. The preferred acid is dry hydrogen chloride and the molar quantity of acid added to the solution of paroxetine free base and carrier may either be in stoichiometric proportion to the paroxetine free base or be in excess of the molar quantity of the paroxetine free base, especially when added as a gas. For example, the preferred range of hydrogen chloride added is, but not limited to, from about 1.0 to about 1.8 times the molar quantity of paroxetine free base. Although dry hydrogen chloride is readily added as a gas the preferred method to add the hydrogen chloride is in the form of hydrogen chloride dissolved into a non-aqueous solvent, preferably hydrogen chloride saturated methanol or ethanol. It is understood that upon addition of the acid, the formed free base salt remains dissolved in solution with the polymeric carrier.

Lastly, upon formation of the free base salt, the process proceeds by (4) recovering the non-aqueous solvent to form a solid state dispersion of the free base salt in the polymeric carrier. Any method of removal of the non-aqueous solvent which renders a homogeneous solid state dispersion is intended, although preferred are methods of evaporation under vacuum. Preferred methods of evaporation under vacuum include rotoevaporation, static vacuum drying and the combination thereof. It is understood that one skilled in the art of pharmaceutical formulations can determine a reasonable temperature at which the non-aqueous solvent can be removed, provided the temperature is not so high as to cause degradation or decomposition of the materials; however, it is preferred that evaporation occurs at about 20° C. to about 50° C. It is also preferred that evaporation of the non-aqueous solvent renders a solid state dispersion which is homogeneous and substantially free of non-aqueous solvent. By substantially free it is meant that the solid state dispersion contains less than 20% by weight of residual non-aqueous solvent, preferably less than 10%, more preferably less then 5%, most preferably less then 1%.

The ratio of paroxetine free base to the pharmaceutically acceptable carrier can be varied over a wide range and depends on the concentration of paroxetine required in the pharmaceutical dosage form ultimately administered. However, the preferred range of paroxetine in the solid dispersion is about 16% to about 50% of the total solid dispersion weight, more preferable is about 20% to about 50%, even more preferable is about 25% to about 40%, most preferable is about 33% of the total dispersion weight.

Alternatively, the general method for preparation of a solid dispersion can proceed by a fusion process wherein a water soluble pharmaceutically acceptable polymeric carrier is mixed with a poorly water soluble drug, preferably paroxetine free base, or drug combination, to form an intimate mixture. The mixture is heated at or near the temperature of the highest melting point of either the pharmaceutically acceptable carrier or poorly water soluble drug or drug combination, thus forming a melt. A preferred polymeric carrier is polyethylene glycol. A preferred ratio by weight of water soluble pharmaceutically acceptable polymeric carrier to poorly water soluble drug is in the range of about 5:1 to about 1:1; preferably about 4:1 to about 1:1; more preferably about 3:1 to about 1.5:1; most preferably about 2:1.

It is understood that the addition of a poorly soluble drug is not limited to one drug but might encompass a combination of one or more drugs provided at least one drug is a poorly water soluble drug in the form of a free base. It is preferred that the poorly water soluble drug in the form of a free base is paroxetine.

Alternatively, the water soluble pharmaceutically acceptable polymeric carrier can be heated to molten condition upon which the poorly water soluble drug, as the free base, can be added to the molten carrier, thus forming a molten homogeneous melt.

Upon forming said molten homogeneous melt the process proceeds by (2) diffusing dry hydrogen chloride gas through the molten drug/carrier mixture to effect salt formation of the drug.

Lastly, upon formation of the free base salt, the process proceeds by (4) cooling the molten homogeneous melt by conventional methods to form a water soluble solid state dispersion.

The ratio of paroxetine free base to the pharmaceutically acceptable carrier can be varied over a wide range and depends on the concentration of paroxetine required in the pharmaceutical dosage form ultimately administered. However, the preferred range of paroxetine in the solid dispersion is about 16% to about 50% of the total solid dispersion weight, more preferable is about 20% to about 50%, even more preferable is about 25% to about 40%, most preferable is about 33% of the total dispersion weight.

Alternatively, the general method for preparation of a solid dispersion can proceed by a combination of the fusion method and the solvent method.

Specifically, the poorly water soluble drug is paroxetine; for the fusion process the preferred pharmaceutically acceptable carrier is polyethylene glycol; for the solvent process

the preferred pharmaceutically acceptable carrier is polyvinylpyrrolidone or polyethylene glycol, the preferred solvent is ethanol, the preferred pharmaceutically acceptable salt is hydrogen chloride, the preferred method to add the hydrogen chloride is in the form of ethanolic hydrogen chloride and the preferred method to recover the solvent is by evaporation at about 20° C. to about 50° C. by a combination of evaporation and static vacuum drying.

The present invention also provides a pharmaceutical composition comprising pharmaceutically acceptable excipients and a solid state dispersion of paroxetine hydrochloride and pharmaceutically acceptable polymeric carrier. Examples of pharmaceutically acceptable excipients include diluents, binders, disintegrants, coloring agents, flavoring agents, lubricants and/or preservatives. The pharmaceutical composition may be formulated by conventional methods of admixture such as blending, filling, granulation and compressing. These agents may be utilized in conventional manner, for example in a manner similar to that already used clinically for anti-depressant agents.

The composition is usually presented as a unit dose composition containing from 1 to 200 mg, more usually from 5 to 100 mg, for example 10 to 50 mg such as 12.5, 20, 25, or 30 mg. Such composition is normally taken from 1 to 6 times daily, for example 2,3, or 4 times daily so that the total amount of active agent administered is within the range of 5 to 400 mg.

Preferred unit dosage forms include tablets or capsules.

The invention also provides for a method of treatment of depression in mammals including humans which method comprises administering an effective amount of pharmaceutically acceptable solid state dispersion of paroxetine hydrochloride.

The invention further provides a solid state dispersion of paroxetine hydrochloride for use in the treatment of depression.

The following examples illustrate the invention. Examples 1–16, show the preparation of solid state dispersions while Examples 17 and 18 show pharmaceutical compositions.

## EXAMPLE 1

PEG-8000/Paroxetine Free-Base, 2:1 wt Basis; Fusion Method

To a 50 mL pear-shaped round bottom flask (equipped with a small magnetic stir bar, rubber septa and a glass pipette) was added PEG-8000 (2.009 g) and paroxetine free-base (0.75 g). The flask was immersed into a water bath, which was heated to a temperature to effect melting of the PEG. Once free-flowing, the glass pipette was carefully lowered below the level of the melt, and a stream of hydrogen chloride gas (dried through conc. sulfuric acid) was bubbled through the pipette for 30 minutes. Stirring was maintained during this process. After the gas introduction, the pipette and the stir bar were removed and the mixture was allowed to cool to room temperature overnight. The solidified product was carefully scraped from the flask. This material could be optionally ground/milled to a desirable particle size.

$^1$H NMR analysis ($CDCl_3$) were wholly consistent with a mixture of PEG and paroxetine hydrochloride, and shows the expected resonance for PEG (3.63, m) and the characteristic signal for paroxetine hydrochloride (2.03, br. d)

Elemental Analysis: Calcd. for 2.009 : 0.83 (wt. basis) PEG-8000 and paroxetine HCl: % C, 56.82; % H, 8.07; % N, 1.04; % Cl, 2.83. Found: % C, 56.71; % H, 8.28; % N, 1.00; % Cl, 3.44.

## EXAMPLE 2

PEG-8000/Paroxetine Free-Base, 2:1 wt Basis; Solution Method

To a 200 mL round bottom flask (equipped with a small magnetic stir bar, rubber septa) was added PEG-8000 (10.0 g) and methanol (140 mL). Paroxetine free-base (4.994 g) was added and stirred about 5 minutes until completely dissolved.

In a separate procedure, methanolic HCl was prepared by bubbling gaseous HCl (9.81 g) into weighed solution of methanol (50 mL). This standard solution (0.196 g/mL) could be used for other experiments.

Methanolic HCl (5 ml), prepared above, was added to the 200 mL flask and stirring continued for 10 minutes. The stir-bar was removed, the flask was placed on a rotary evaporator and concentrated with a bath temperature at 35° C. Once a thick paste was obtained the flask was placed under static high pressure vacuum, which was continued 18 hours. On occasion, the material was scraped free from the sides of the flask to assist in the removal of residual volatiles. The product was scraped from the flask and could be ground/milled to an acceptable particle size.

$^1$H NMR analysis ($CDCl_3$) were wholly consistent with a mixture of PEG and paroxetine hydrochloride, and shows the expected resonance for PEG (3.63, m) and the characteristic signal for paroxetine hydrochloride (2.03, br. d). No residual methanol was detected.

Elemental Analysis: Calcd. for 10.000: 5.54 (wt. basis) PEG-8000 and paroxetine HCl: % C, 57.31; % H, 7.86; % N, 1.27; % Cl, 3.43. Found: % C, 57.31; % H, 8.07; % N, 1.21; % Cl, 4.38.

## EXAMPLE 3

PEG-8000/Paroxetine Free-Base, 4:1 wt Basis, Solution Method

Using PEG-8000 (4.013 g) and paroxetine free-base (1.015 g), and methanolic HCl (1 mL of a 0.19 g/mL solution) and the method of Example 2, a solid dispersion of PEG/paroxetine hydrochloride 4:1 wt basis was prepared.

$^1$H NMR analysis ($CDCl_3$) were wholly consistent with a mixture of PEG and paroxetine hydrochloride, and shows the expected resonance for PEG-8000 (3.63, m) and the characteristic signal for paroxetine hydrochloride (2.03, br. d). No residual methanol was detected.

Elemental Analysis: Calcd. for 4.013:1.126 (wt. basis) PEG-8000 and paroxetine HCl: % C, 56.23; % H, 8.32; % N, 0.78; % Cl, 2.11. Found: % C, 56.11; % H, 8.60; % N, 0.72; % Cl, 2.63.

## EXAMPLE 4

PEG-8000/Paroxetine Free-Base, 1:1 wt Basis, Solution Method using ethanolic HCl

An ethanolic HCl solution was prepared by bubbling HCl gas (3.23 g) into a solution (50 mL) of absolute ethanol.

Using PEG-8000 (2.007 g) and paroxetine free-base (2.066 g), in a mixture of ethanol (15 mL) and methanol (8 mL), was added ethanolic HCl (3 mL) and the method of Example 2, a solid dispersion of PEG/paroxetine hydrochloride 1:1 wt basis was prepared.

$^1$H NMR analysis ($CDCl_3$) were wholly consistent with a mixture of PEG and paroxetine hydrochloride, and shows the expected resonance for PEG (3.63, m) and the characteristic signal for paroxetine hydrochloride (2.03, br. d). 5% residual ethanol (wt basis) was detected.

Elemental Analysis: Calcd. for 2.007:2.292 (wt. basis) PEG-8000 and paroxetine HCl: % C, 58.77; % H, 7.29; % N, 1.90; % Cl, 5.15. Found: % C, 59.18; % H, 7.72; % N, 1.98; % Cl, 4.95.

EXAMPLE 5

PVP 29/32K/Paroxetine Free-Base, 2:1 wt Basis, Solution Method

Using PVP 29/32K (2.077 g), paroxetine free-base (1.008 g), methanol (28 mL), methanolic HCl (1.0 mL of a 0.196 g/mL solution) and the method of Example 2, a solid dispersion of PVP/paroxetine hydrochloride, 2:1 wt basis, was prepared.

$^1$H NMR analysis ($CDCl_3$) were wholly consistent with a mixture of PVP and paroxetine hydrochloride, and shows the expected resonances for PVP (series of br. m 3.4–1.6) and the characteristic signal for paroxetine hydrochloride (2.03, br. d). 4% methanol (wt basis) was detected.

Elemental Analysis: Calcd. for 2.077:1.118 (wt. basis) PVP and paroxetine HCl: % C, 61.13; % H, 7.74; % N, 8.82; % Cl, 5.89. Found: % C, 62.49; % H, 7.63; % N, 9.12; % Cl, 6.33.

EXAMPLE 6

PEG-8000/Paroxetine Free-Base, 2:1 wt Basis; Solution Method

As in Example 2, using ethanol instead of methanol as solvent, ethanolic HCl (solution prepared in Example 4), PVP 29/32K /paroxetine free-base, 2.006:1.048 (wt basis).

$^1$H NMR analysis ($CDCl_3$) were wholly consistent with a mixture of PVP and paroxetine hydrochloride, and shows the expected resonances for PVP (series of br. m 3.4–1.6) and the characteristic signal for paroxetine hydrochloride (2.03, br. d). 14% ethanol (wt basis) was detected.

Elemental Analysis: Calcd. for 2.006:1.048:0.124 (wt. basis) PVP/paroxetine HCl/ HCl: % C, 59.96; % H, 7.23; % N, 8.59; % Cl, 7.07. Found: % C, 61.39; % H, 7.32; % N, 8.67; % Cl, 7.96.

Using the methods described above and modifications thereof the following additional examples could be prepared by one skilled in the art:

| Example | Excipient | Ratio[1] | HCl equivalent | Method[2] |
|---|---|---|---|---|
| 7 | PVP | 1/1 | 1.0 | Solution |
| 8 | PVP | 2/1 | 1.0 | Solution |
| 9 | PVP | 3/1 | 1.0 | Solution |
| 10 | PEG | 1/1 | 1.0 | Solution |
| 11 | PEG | 2/1 | 1.0 | Solution |
| 12 | PEG | 3/1 | 1.0 | Solution |
| 13 | PEG | 4/1 | 1.0 | Solution |
| 14 | PEG | 1/1 | excess | Fusion |
| 15 | PEG | 3/1 | excess | Fusion |
| 16 | PEG | 4/1 | excess | Fusion |

[1]Weight basis of Excipient to Paroxetine free-base
[2]See Example 2 for Solution Method, Example 1 for Fusion.

Dosage and Formulation

The method of this invention can be administered by any means that produces contact of the active agent with the agent's site of action, serotonin re-uptake inhibition, in the body of a mammal. They can be administered by any conventional means available for use in conjunction with pharmaceuticals, either as individual therapeutic agents or in a combination of therapeutic agents.

The dosage of the novel compounds of this invention administered will, of course, vary depending upon known factors, such as the pharmacodynamic characteristics of the particular agent and its mode and route of administration; the age, health and weight of the recipient; the nature and extent of the symptoms; the kind of concurrent treatment; the frequency of treatment; and the effect desired. A daily dosage of active ingredient can be expected to be about 0.001 to 10 milligrams per kilogram of body weight.

Dosage forms (compositions suitable for administration) contain from about 0.1 milligram to about 100 milligrams of active ingredient per unit. In these pharmaceutical compositions the active ingredient will ordinarily be present in an amount of about 0.5–50% by weight based on the total weight of the composition.

The active ingredient can be administered orally in solid dosage forms, such as capsules, tablets, and powders.

Gelatin capsules contain the active ingredient and powdered carriers, such as lactose, starch, cellulose derivatives, magnesium stearate, stearic acid, and the like. Similar diluents can be used to make compressed tablets. Both tablets and capsules can be manufactured as sustained release products to provide for continuous release of medication over a period of hours. Compressed tablets can be sugar coated or film coated to mask any unpleasant taste and protect the tablet from the atmosphere, or enteric coated for selective disintegration in the gastrointestinal tract.

Suitable pharmaceutical excipients are described in *Remington's Pharmaceutical Sciences,* Mack Publishing Company, a standard reference text in this field.

Useful pharmaceutical dosage-forms for administration of the compounds of this invention can be illustrated as follows:

Capsules

A large number of unit capsules are prepared by filling standard two-piece hard gelatin capsules each with 10 milligrams of powdered active ingredient, 150 milligrams of lactose, 50 milligrams of cellulose, and 6 milligrams magnesium stearate.

Soft Gelatin Capsules

A mixture of active ingredient in a digestible oil such as soybean oil, cottonseed oil or olive oil is prepared and injected by means of a positive displacement pump into gelatin to form soft gelatin capsules containing 10 milligrams of the active ingredient. The capsules are washed and dried.

Tablets

A large number of tablets are prepared by conventional procedures so that the dosage unit was 10 milligrams of active ingredient, 0.2 milligrams of colloidal silicon dioxide, 5 milligrams of magnesium stearate, 275 milligrams of microcrystalline cellulose, 11 milligrams of starch and 98.8 milligrams of lactose. Appropriate coatings may be applied to increase palatability or delay absorption.

The following examples further illustrate a specific embodiment of the present invention, and is considered an illustrative, but not limiting, description of the invention.

EXAMPLE 17

A 20 mg paroxetine base (as the HCl salt) tablet using a solid dispersion as described in Example 8

| Ingredient | mg/tablet | gm/1000 tablet batch |
|---|---|---|
| Paroxetine HCl* | 22.21 | 22.21 |
| Polyvinylpyrrolidone* | 40.00 | 40.00 |
| Dibasic dicalcium phosphate dihydrate | 210.79 | 210.79 |
| Sodium Starch Glycolate | 24.00 | 24.00 |
| Magnesium Stearate | 3.00 | 3.00 |
| Total | 300 mg | 300 gm |

*Theoretical quantities for a solid dispersion of Paroxetine HCl and polyvinylpyrrolidone as described in Example #8.

Procedure: Mill the paroxetine HCl/polyvinylpyrrolidone solid dispersion by passing through a 20 mesh screen. Blend the milled solid dispersion with the dibasic dicalcium phos-

phate dihydrate, sodium starch glycolate and magnesium stearate. Compress tablets to a weight of 300 mg with a tablet hardness of approximately 17 Strong-Cobb Units.

## EXAMPLE 18

A 20 mg Paroxetine Base (as the HCl Salt) Tablet using a Solid Dispersion as Described in Example 11

| Ingredient | mg/tablet | gm/1000 tablet batch |
|---|---|---|
| Paroxetine HCl* | 22.21 | 22.21 |
| Polyethylene glycol* | 40.00 | 40.00 |
| Dibasic dicalcium phosphate dihydrate | 210.79 | 210.79 |
| Sodium Starch Glycolate | 24.00 | 24.00 |
| Magnesium Stearate | 3.00 | 3.00 |
| Total | 300 mg | 300 gm |

*Theoretical quantities for a solid dispersion of Paroxetine HCl and polyethylene glycol as described in Example #11.

Procedure: Mill the paroxetine HCl/polyethylene glycol solid dispersion by passing through a 20 mesh screen. Blend the milled solid dispersion with the dibasic dicalcium phosphate dihydrate, sodium starch glycolate and magnesium stearate. Compress tablets to a weight of 300 mg with a tablet hardness of approximately 17 Strong-Cobb Units.

What is claimed is:

1. A process for preparing a water soluble solid state dispersion of paroxetine salt and a pharmaceutically acceptable polymeric carrier, which process comprises:

(a) forming a solution of a water soluble pharmaceutically acceptable polymeric carrier and a non-aqueous solvent,

(b) dissolving paroxetine free base into the solution, wherein the ratio by weight of water soluble pharmaceutically acceptable polymeric carrier to paroxetine is in the range of about 4:1 to about 1:1;

(c) contacting the paroxetine free base in solution with at least one equivalent of an acid, wherein the acid is a non-toxic inorganic or organic acid, to form a pharmaceutically acceptable non-crystalline paroxetine salt anhydrate in solution; and

(d) removing non-aqueous solvent by evaporation under vacuum.

2. The process of claim 1 wherein said polymeric carrier is selected from one or more of the following: polyvinylpyrrolidone, hydroxypropylmethyl cellulose, hydroxypropyl cellulose, methyl cellulose, block co-polymers of ethylene oxide and propylene oxide, and polyethylene glycol.

3. The process of claim 1 wherein paroxetine free base is dissolved into a non-aqueous solvent before the polymeric carrier is dissolved into the non-aqueous solvent.

4. The process of claim 1 wherein the non-aqueous solvent is an alcohol selected from methanol, ethanol, n-propanol, iso-propanol, n-butanol, iso-butanol, and sec-butanol.

5. The process of claim 1 wherein the non-aqueous solvent is ethanol.

6. The process of claim 1 wherein the acid is hydrogen chloride in the form of dry hydrogen chloride gas or dry hydrogen chloride dissolved into a non-aqueous solvent.

7. The process of claim 1

wherein said polymeric carrier is polyvinylpyrrolidone.

8. The process of claim 7 wherein the polymeric carrier is polyvinylpyrrolidone having an average molecular weight of from about 2,500 to about 3,000,000.

9. The process of claim 7 wherein the non-aqueous solvent is an alcohol selected from methanol, ethanol, n-propanol, iso-propanol, n-butanol, iso-butanol, and sec-butanol.

10. The process of claim 7 wherein the non-aqueous solvent is ethanol.

11. The process of claim 7 wherein the acid is hydrogen chloride in the form of dry hydrogen chloride gas or dry hydrogen chloride dissolved into a non-aqueous solvent.

12. The process of claim 7

wherein said solvent is ethanol, said acid is dry hydrogen chloride, and wherein the dry hydrogen chloride is dissolved in methanol or ethanol, to form pharmaceutically acceptable paroxetine hydrogen chloride in solution.

13. A solid state dispersion of a pharmaceutically acceptable polymeric carrier and noncrystalline paroxetine hydrochloride anhydrate produced by the process of claim 12.

14. The process of claim 1

wherein said polymeric carrier is polyethylene glycol and said acid is a non-toxic inorganic or organic acid.

15. The process of claim 14 wherein the polymeric carrier is polyethylene glycol having an average molecular weight of from about 1,000 to about 20,000.

16. The process of claim 14 wherein the non-aqueous solvent is an alcohol selected from methanol, ethanol, n-propanol, iso-propanol, n-butanol, iso-butanol, and sec-butanol.

17. The process of claim 14 wherein the non-aqueous solvent is ethanol.

18. The process of claim 14 wherein the acid is hydrogen chloride in the form of dry hydrogen chloride gas or dry hydrogen chloride dissolved into a non-aqueous solvent.

19. The process of claim 14 wherein said solvent comprises

ethanol, said acid is dry hydrogen chloride, wherein the dry hydrogen chloride is dissolved in methanol or ethanol and said removing non-aqueous solvents comprises removing ethanol and, if present, methanol.

20. A solid state dispersion of a pharmaceutically acceptable polymeric carrier and noncrystalline paroxetine hydrochloride anhydrate produced by the process of claim 1.

21. A process for preparing a water soluble solid state dispersion of paroxetine and a pharmaceutically acceptable polymeric carrier, which process comprises:

(a) contacting a water soluble pharmaceutically acceptable polymeric carrier with paroxetine free base to form an intimate mixture, wherein the ratio by weight of water soluble pharmaceutically acceptable polymeric carrier to paroxetine free base is in the range of about 4:1 to about 1:1;

(b) heating the mixture to form a molten homogeneous melt of polymeric carrier and paroxetine free base;

(c) contacting the molten homogeneous melt of polymeric carrier and paroxetine free base with at least one equivalent of dry hydrogen chloride to form pharmaceutically acceptable noncrystalline paroxetine hydrogen chloride anhydrate in the molten homogeneous melt; and

(d) cooling the molten homogeneous melt to form a water soluble solid state dispersion.

22. A process for preparing a water soluble solid state dispersion of paroxetine and a pharmaceutically acceptable polymeric carrier, which process comprises:

(a) contacting a polyethylene glycol with paroxetine free base to form an intimate mixture, wherein the ratio by weight of polyethylene glycol to paroxetine free base is in the range of about 4:1 to about 1:1;

(b) heating the mixture to form a molten homogeneous melt of polyethylene glycol and paroxetine free base;

(c) contacting the molten homogeneous melt of polyethylene glycol and paroxetine free base with at least one equivalent of dry hydrogen chloride to form pharmaceutically acceptable noncrystalline paroxetine hydrogen chloride anhydrate in the molten homogeneous melt; and

(d) cooling the molten homogeneous melt to form a water soluble solid state dispersion.

**23**. A solid state dispersion comprising a pharmaceutically acceptable polymeric carrier and noncrystalline paroxetine salt anhydrate.

**24**. A pharmaceutical composition comprising a solid state dispersion of claim **23** and one or mote pharmaceutically acceptable excipients.

**25**. A pharmaceutical composition comprising a solid state dispersion of claim **20** and one or more pharmaceutically acceptable excipients.

**26**. A method of treating depression in a warm-blooded animal comprising administering to said animal a solid state dispersion as defined in claim **23**, the amount of paroxetine hydrochloride in said dispersion being effective for treating depression.

**27**. A method of treating depression in a warm-blooded animal comprising administering to said animal a solid state dispersion as defined in claim **20**, the amount of paroxetine hydrochloride in said dispersion being effective for treating depression.

* * * * *

# United States Patent [19]

**Christensen et al.**

[11] **3,912,743**

[45] **Oct. 14, 1975**


[54] **4-PHENYLPIPERIDINE COMPOUNDS**


[75] Inventors: **Jorgen Anders Christensen**, Virum; **Richard Felt Squires**, Gl. Olstykke, both of Denmark

[73] Assignee: **A/S Ferrosan**, Denmark



[22] Filed: **Jan. 21, 1974**

[21] Appl. No.: **435,006**

[30] **Foreign Application Priority Data**

Jan. 30, 1973 United Kingdom..... 4496/73

[52] **U.S. Cl.** ..... **260/293.58**; 260/293.73; 260/293.81; 260/293.83; 260/293.84; 424/267

[51] **Int. Cl.²**..... **C07D 211/22**

[58] **Field of Search**..... 260/293.58, 293.83



[56] **References Cited**

UNITED STATES PATENTS

| | | | |
|---|---|---|---|
| 2,976,291 | 3/1961 | Jacob et al. | 260/294.7 |
| 3,178,438 | 4/1965 | Clarke | 260/294.7 |



*Primary Examiner*—G. Thomas Todd
*Attorney, Agent, or Firm*—Wenderoth, Lind & Ponack



[57] **ABSTRACT**

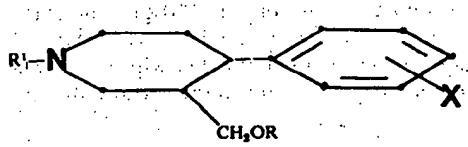
The invention relates to new 3-substituted 1-alkyl-4-phenylpiperidines, being useful as antidepressant and anti-Parkinson agents, and to their production.


**8 Claims, No Drawings**

## 4-PHENYLPIPERIDINE COMPOUNDS

The present invention relates to novel 4-phenylpiperidine compounds and their salts with pharmaceutically acceptable acids, that are useful as pharmacological agents and to means for their production.

More particularly the invention relates to 3-substituted 1-alkyl-4-phenylpiperidine compounds having the general formula:



(I)

wherein R represents an alkyl or alkynyl group having 1–4 carbon atoms, or a phenyl group optionally substituted by lower alkyl, alkylthio, alkoxy, halogen, nitro, acylamino, methylsulfonyl, methylenedioxy, or tetrahydronaphthyl, $R^1$ represents alkyl or alkynyl, and X represents hydrogen, alkyl having 1–4 carbon atoms, alkoxy, trifluoroalkyl, hydroxy, halogen, methylthio, or aralkyloxy.

Where not otherwise specified, the alkyl, alkynyl, and acyl groups are preferably having 1–4 carbon atoms. The aromatic part of the aralkoxy group is preferably unsubstituted phenyl.

Examples of alkyl groups are methyl, ethyl, propyl, isopropyl, n-butyl, and tert.butyl, also as parts of the alkoxy and alkylthio groups.

Examples of alkynyl groups are ethynyl, propynyl, and butynyl groups.

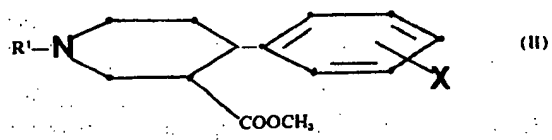
Examples of halogens are chlorine, bromine, and fluorine.

Examples of acylamino groups are acetylamino, propylamino, and butylamino.

The salt forming acids may be any of the available, pharmaceutically acceptable acids.

The compounds of this invention have interesting pharmacological properties which make them useful as antidepressants and anti-Parkinson agents. The compounds, wherein R is phenyl, 4-methoxyphenyl, and 1,3-benzdioxylyl, have proved particularly valuable in the said respects.

The compounds of formula I are prepared from the corresponding carbinols which can be prepared by reducing a compound of the formula II



(II)

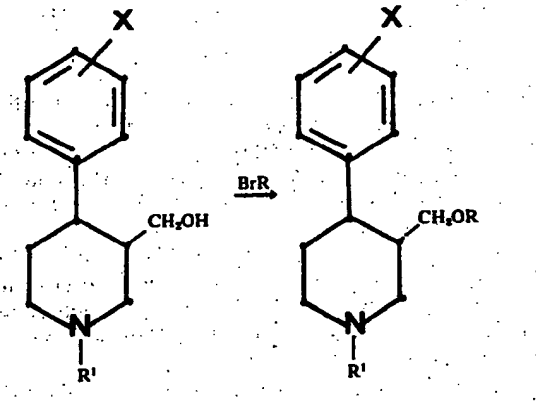
where $R^1$ and X are as hereinbefore defined, preferably with a complex metal hydride reducing agent, especially lithium aluminium hydride.

Compounds having the formula II may be prepared according to J. T. Plati, A. K. Ingberman and W. Wenner (J.Org.Chem. 1957; 22, 201) who prepare the compound in which X is hydrogen and $R^1$ is methyl by treating arecoline (methyl-1,2,5,6-tetrahydro-3-pyridine-carboxylate) with phenyl magnesium bromide.

In the same manner, other compounds used as starting material for the desired piperidine carbinols are prepared using the appropriate arecoline homologue and X-phenyl magnesium bromide. The reaction gives the two isomers, the cis form ($\alpha$) and the trans form ($\beta$) (carbon atoms 3 and 4 in the piperidine ring). Both forms can again be resolved into a (+) and a (−) form.

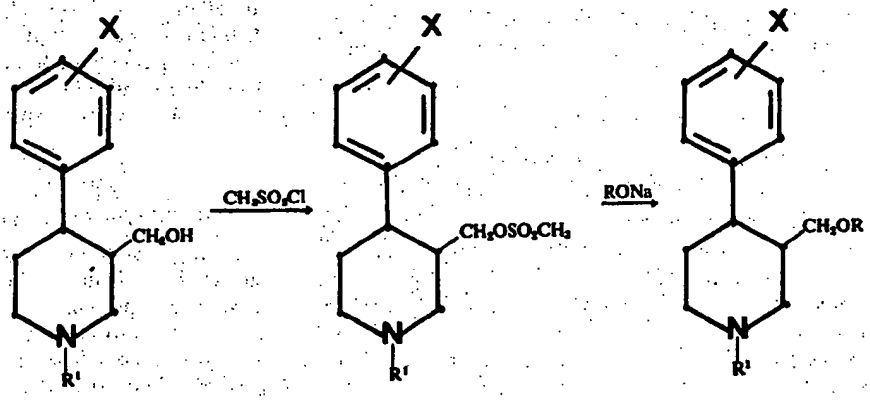
The compounds of the invention may be prepared from the piperidine carbinols using different processes.

Method A



The alkali metal compound of the piperidine carbinol is treated with an active ester corresponding to the desired R substituent.

Method B



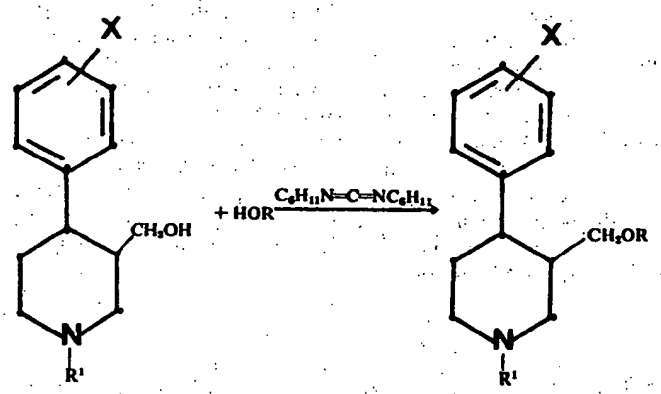
The piperidine carbinol is converted into an ester, e.g. the methane sulfonic ester, using methane sulfochloride in pyridine, and reacting with RONa, R being as above.

Using method A, the α-form of the carbinol gives the α-form of the ether, whereas the β-form of the carbinol gives the β-form of the ether.

Using method B, the α-form of the carbinol gives the α-form of the ether, but surprisingly the β-form of the carbinol gives a mixture of the α-form and the β-form, mainly the α-form.

Method C

Two hydroxy compounds are condensed using dicyclohexylcarbodiimide as a condensing agent:




In this method the α-carbinols give α-ethers, and the β-carbinols give a mixture of α- and β-ethers.

According to another method the compounds of the invention are prepared from compounds of formula I, wherein R and X are as defined previously, and $R^1$ in this case is hydrogen or an acyl group.

If $R^1$ is hydrogen, the compound is alkylated, and if $R^1$ is an acyl group, the group is reduced to give the corresponding alkyl group, or the acyl group is removed by hydrolyzing to leave the NH group which is then alkylated.

Usually one of the optical active forms of the new compounds is therapeutically more active than the other. To isolate this form the resolution may be accomplished as described in Example 3, or the resolution may be accomplished at an earlier stage, before the carbinol group of the piperidine is converted to an ether group.

The following Examples are illustrative of the compounds of the invention and their preparation without being limiting.

## EXAMPLE 1

### 3-((4-Methoxyphenoxy)-methyl)-1-methyl-4-phenylpiperidine hydrochloride

*a.* Methane sulfochloride (55.5 g) was added dropwise to a solution of 3-hydroxymethyl-1-methyl-4-phenylpiperidine (88.8 g) in dry pyridine (300 ml), the temperature being kept between 10° and 15°C, and the mixture being stirred for 1 hour. The reaction mixture was poured into a mixture of sodium hydroxide (15 g), water (500 ml), ice (500 g), and ether (400 ml). The ether layer was separated, and the aqueous layer was extracted with ether. The ether extracts were added to the ether layer, washed with water and dried over potassium carbonate. Removal of the solvent in vacuo (maximum 25°C) gave the methanesulfonic acid ester as an oil. Yield 120 g.

*b.* To a solution of sodium (17.5 g) in dry methanol (210 ml) was added a solution of 4-methoxyphenol (87.5 g) in methanol (140 ml) and a solution of the methanesulfonic ester of 3-hydroxymethyl-1-methyl-4-phenylpiperidine (105 g) in methanol (200 ml). The mixture was stirred and refluxed for 16 hours. After removal of the solvent in vacuo, the evaporation residue was poured into a mixture of ice (150 g), water (150 ml), and ether (200 ml). The ether layer was separated, and the aqueous layer was extracted with ether. The combined ether solutions were washed with water and agitated with 2N hydrochloric acid (200 ml) to give a crystalline precipitate which was dried. Yield 56.8 g. M.p. 236°–239°C.

Recrystallization from 97% ethanol gave 52.3 g of 3-((4-methoxyphenoxy)-methyl)-1-methyl-4-phenylpiperidine hydrochloride, m.p. 237°–239°C.

## EXAMPLE 2

### 3-Methoxymethyl-1-methyl-4-phenylpiperidine

To a solution of sodium (15.2 g) in methanol (270 ml) was added a solution of the methanesulfonic acid ester of 3-hydroxymethyl-1-methyl-4-phenylpiperidine (121 g) in methanol (270 ml). The mixture was stirred and refluxed for 16 hours. The solvent was removed in vacuo, and the evaporation residue was poured into ice-water. The mixture was extracted with ether, the ether extract was dried over potassium carbonate, and the ether was evaporated. The evaporaton residue was distilled in vacuo to give 66 g of 3-methoxymethyl-1-methyl-4-phenylpiperidine. B.p. 0.05 mm: 78°–81°C. The hydrochloride of this compound has m.p. 151°–154°C, and the hydrobromide has m.p. 158°C.

## EXAMPLE 3

### Resolution of racemic 3-methoxymethyl-1-methyl-1-4-phenylpiperidine

*a.* To a solution of (−)dibenzoyltartaric acid (7.1 g) in 99% ethanol (75 ml) was added (±)e-methoxymethyl-1-methyl-4-phenylpiperidine (8.8 g). After evaporation of the solvent the evaporation residue was recrystallized from benzene (80 ml) to give 5 g of the dibenzoyltartrate, m.p. 152–154°C. This was dissolved in a mixture of 4N sodium hydroxyde (10 ml) and ether (20 ml), and the ether layer was separated,

dried over potassium carbonate, and evaporated to dryness. The evaporation residue was treated with hydrobromic acid, the water removed in vacuo, and the residue recrystallized from ethanol and ether to yield the hydrobromide, m.p. 178–180°C. $[\alpha]_{25}^{D}=+36$ ($c=7\%$ in 99% ethanol).

*b.* The benzene from the recrystallization mentioned under (*a*) above was evaporated, and the evaporation residue dissolved in a mixture of 4N sodium hydroxyde (20 ml) and ether (20 ml). The ether layer was separated, dried over potassium carbonate, and evaporated. The residue (4.6 g) was added to a solution of (+)dibenzoyltartaric acid (3.7 g) in 99% ethanol (40 ml), whereupon the procedure was as described under a). The hydrobromide has m.p. 179°–180°C, and $[\alpha]_{25}^{D}=-37$ ($c=7\%$ in 99% ethanol).

## EXAMPLE 4

(α)-3-Methoxymethyl-1-methyl-4-phenylpiperidine

(α)-3-hydroxymethyl-1-methyl-4-phenylpiperidine (6.15 g) was added to a suspension of sodium hydride (1.6 g), (50% in oil) in dry dimethylformamide. The mixture was stirred, and a solution of methylbromide (2.85 g) in dimethylformamide (10 ml) was slowly added, the stirring being continued for 16 hours at 25°C. 40 ml of water were added, and the reaction mixture was extracted 5 times with methylene chloride (25 ml). The combined methylene chloride extracts were extracted with 0.5N hydrochloric acid, and the extract was made alkaline with 4N sodium hydroxyde (10 ml) and extracted with ether. The ether extract was dried over potassium carbonate, the ether was removed by distillation, and the residue was distilled in vacuo to yield 4 g of (α)-3-methoxymethyl-1-methyl-4-phenylpiperidine, b.p. 72°–74°C (0.05 mm).

With hydrobromic acid, the hydrobromide was prepared, m.p. 158°–160°C.

## EXAMPLE 5

(β)-3-Methoxymethyl-1-methyl-4-phenylpiperidine hydrobromide

The procedure described in Example 4 was followed except that the (β)-3-hydroxymethyl compound was used instead of the (α) compound.

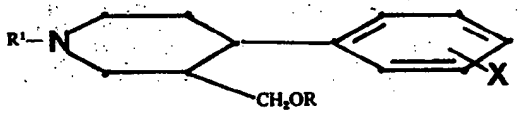
The hydrobromide obtained had m.p. 201–204°C.

## EXAMPLE 6

A mixture of 16.5 g of α-3-hydroxymethyl-1-methyl-4-phenylpiperidine, 12.5 g of 4-methoxyphenol and 16.5 g of dicyclohexylcarbodiimide was heated to 160°–180°C for 24 hours. After cooling, 200 ml of ether were added to dissolve the product. The separated dicyclohexylurea was removed by tiltration, and the solution was extracted with 200 ml of 0.5N hydrochloric acid. From the acid solution, the hydrochloride of the α-compound was prepared in the usual way.

## EXAMPLES 7–67

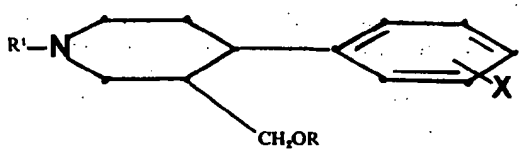
Using one or the other of the methods described in Examples 1–6, the compounds listed below were prepared:




α - forms R¹ = Methyl

| Code | R | X | M.p. (°C) | Salt |
|---|---|---|---|---|
| GF 01 | Methyl | H | 151–154 | HCl |
| | | | 160–166 | HBr |
| | | racemic form | 179–180 | HBr |
| GF 02 | Ethyl | H | 169–171 | HCl |
| GF 03 | Methyl | 2-Methyl | 189–190 | HBr |
| GF 04 | Methyl | 4-Fluor | 123–130 | HBr |
| GF 05 | Methyl | 2-Methoxy | 171–174 | HBr |
| GF 06 | Methyl | 3-Trifluormethyl | 92–94 | maleate |
| | | racemic form | 129–131 | HBr |
| GF 07 | Methyl | 4-tert.butyl | 143–145 | maleate |
| GF 08 | Methyl | 3-Methoxy | 100–102 | maleate |
| GF 09 | Methyl | 4-Chloro | 104–105 | maleate |
| GF 10 | 2-Propyl | H | 179–181 | HCl |
| GF 11 | Methyl | 3-Hydroxy | 222–223 | HCl |
| GF 12 | Methyl | 4-Methoxy | 103–104 | maleate |
| GF 13 | Methyl | 4-Hydroxy | 230–233 | HCl |
| GF 14 | t.-Butyl | H | 195–197 | HBr |
| GF 15 | Phenyl | H | 220–223 | HBr |
| GF 16 | 4-Chlorophenyl | H | 199–202 | HBr |
| GF 17 | 4-Methoxyphenyl | H | 234–235 | HBr |
| GF 18 | 2-Methoxyphenyl | H | 164–166 | HBr |
| GF 19 | 3-Methoxyphenyl | H | 176–179 | HBr |
| GF 20 | 4-Ethoxyphenyl | H | 185–187 | HBr |
| GF 21 | 3,5-Dimethoxyphenyl | H | 166–169 | HBr |
| GF 22 | Methyl | 4-Bromo | 249–250 | HBr |
| GF 23 | 4-Methoxyphenyl | 4-Methoxy | 211–212 | HCl |
| GF 24 | Phenyl | 4-fluoro | 203–206 | HCl |
| GF 25 | Phenyl | 4-Methoxy | 213–215 | HCl |
| GF 26 | 4-Methoxyphenyl | 4-Fluoro | 227–230 | HCl |
| GF 27 | Phenyl | 4-Chloro | 201–203 | HCl |
| GF 28 | 4-Methoxyphenyl | 4-Chloro | 217–219 | HCl |
| GF 29 | 4-Methylsulfonylphenyl | H | 146–148 | HCl |
| GF 30 | 4-Methylthiophenyl | H | 210–212 | HCl |
| GF 31 | 4-Methoxyphenyl | H (−)form | 190–192 | HCl |
| GF 32 | 4-Methoxyphenyl | H (+)form | 191–193 | HCl |
| GF 33 | Phenyl | 4-Methylthio | 222–226 | HCl |
| GF 34 | 4-Methoxyphenyl | 4-Methylthio | 240–242 | HCl |

—Continued



| Code | R | X | M.p. (°C) | Salt |
|---|---|---|---|---|
| | | α - forms | $R^1$ = Methyl | |
| GF 35 | 4-Acetylaminophenyl | H | 243–247 | HCl |
| GF 36 | 4-Methoxyphenyl | H | 110–111 | $(-CH_2COOH)_2$ |
| GF 37 | 2-Propynyl | H | 121–131 | $(=CHCOOH)_2$ |
| GF 38 | 1,3-benzdioxolyl-(5) | H | 244–246 | HCl |
| GF 39 | 2-t.-Butylphenyl | H | 185–188 | HCl |
| GF 40 | 3,4-Dimethoxyphenyl | H | 230–233 | HCl |
| GF 48 | Phenyl | H (−) form | 173–174 | HBr |
| GF 49 | Phenyl | H (+)form | 173–174 | HBr |
| GF 50 | 4-Methoxyphenyl | 4-Hydroxy | 113–115 | HCl |
| GF 51 | 1,3-Benzdioxolyl-(5) | H (+)form | 217 | HCl |
| GF 52 | 1,3-Benzdioxolyl-(5) | H (−)form | 219 | HCl |
| GF 53 | (1,2,3,4-Tetrahydro-naphthyl-(3)) | H | 214–217 | HCl |
| GF 54 | 4-Methoxyphenyl | 4-Benzyloxy | 201–204 | HCl |
| | | $R^1$ = Propynyl | | |
| GF 41 | Methyl | H | 190–191 | HBr |
| GF 42 | 4-Methoxyphenyl | H | 170–172 | HCl |
| | | $R^1$ = H | | |
| GF 55 | 4-Methoxyphenyl | H (+)form | 141–142 | HCl |
| GF 56 | 4-Methoxyphenyl | H (−)form | 142–143 | HCl |
| GF 57 | 1,3-Benzdioxolyl-(5) | H (−)form | 181–182 | HCl |
| GF 58 | 1,3-Benzdioxolyl-(5) | H (+)form | 182–183 | HCl |
| | | $R^1 = -CH_2CF_3$ | | |
| GF 59 | 4-Methoxyphenyl | H (−)form | 123–128 | dec. HCl |
| GF 60 | 4-Methoxyphenyl | H (+)form | 116–120 | dec. HCl |
| GF 61 | 4-Methoxyphenyl | H racemic form | 142–143 | HBr |
| GF 43 | 4-Nitrophenyl | H | 219–224 | HBr |
| GF 44 | 3-Methyl | 4-Chloro | 225–228 | HBr |
| GF 45 | 3-Methyl | H | 201–203 | HBr |
| GF 46 | 4-Acetylaminophenyl | H | 258–262 | HCl |
| GF 47 | 4-Methoxyphenyl | H | 186 | HCl |

As stated hereinbefore, the compounds of formula I are useful as antidepressants and as anti-Parkinson drugs as indicated by their biochemical and pharmacological properties.

At present the antidepressants most used in the clinic are the tricyclic thymoleptics (e.g. Imipramine and Amitriptyline). These drugs act by centrally potentiating serotonin (5HT) and noradrenaline (NA) as a consequence of neuronal reuptake inhibition.

The same potentiating action of the new compounds was confirmed by determinating 5HT- and NA-uptake inhibition in virtro using synaptosomes prepared from different regions of rat brain. Some of the compounds, e.g. GF 32, GF 52, and GF 57, are especially strong inhibitors of 5HT-uptake, while others, e.g. GF 48 and GF 49, are more potent NA-uptake inhibitors. Known tricyclic thymoleptics affect the cardiovascular and peripheral autonomic nervous systems causing a wide range of side-effects. Cardiac disturbances and varying degrees of hypotension occur rather frequently and may be very serious. Compounds according to this invention, e.g. GF 32, are more active 5HT potentiators than is Imipramine, but affect the cardiovascular system less than do the most common tricyclic thymoleptics, and therefore lack the more serious side-effects mentioned.

5HT-uptake inhibitory activity

Antagonism of p-chloroamphetamine (PCA)-induced 5HT-depletion from rat brain:

| Substance | 1) $ED_{50}$ mg/kg s.c. | 2) $ED_{50}$ mg/kg p.o. |
|---|---|---|
| GF 32 | 1.5 | 20 |
| GF 61 | 1.4 | |
| GF 52 | 2.8 | 3.2 |
| GF 57 | 0.5 | 2.0 |
| Imipramine 8.0 | 44 | |
| Chlorimipramine | 1.0 | 42 |
| Amitriptyline | 12 | |
| Protriptyline | >50 | |

1) Test drugs were administered s.c. simultaneously with PCA.
2) Test drugs were administered 2 hours before PCA.

The method is described by Squires (Acta phamacol. et toxicol. 1972, 31 suppl. 1, 35).

In all experiments, GF 32 induced heart bundle branch block at a significantly higher dose level than did the tricyclic thymoleptics.

In dogs, the infusion produced an initial positive inotropic effect. GF 32 showed this property in the dose range 1–25 mg/kg, Imipramine and Amitriptyline at 1–6 mg/kg. Higher doses produced negative inotropic effects, No ECG changes were found in dogs during four weeks of daily administration of GF 32 in doses of 5 and 10 mg/kg.

Some of the new compounds, e.g. GF 15, GF 48, and GF 49, have shown a strong and selective inhibition of dopamine (DA) re-uptake indicating anti-Parkinson activity. Benztropine and some related anti-Parkinson drugs inhibit DA re-uptake, in addition to having strong anticholinergic effects, which may cause some of the most common adverse effects of these compounds. The

compounds of this invention are almost devoid of anticholinergic effect.

Activity as dopamine-potentiators

Potentiation of apomorphine-induced gnawing in mice:

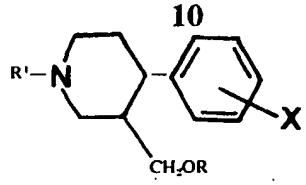
| Substance | $ED_{50}$ mg/kg s.c. | Maximal response |
|---|---|---|
| GF 14 | 7 | 139 |
| GF 15 | 28 | 224 |
| GF 48 | 43 | 126 |
| GF 49 | 27 | 221 |
| Benztropine | °5 | 52 |

The toxicity of the compounds of the invention is about the same as that of the tricyclic thymoleptics, but some compounds, e.g. GF 32, are less toxic.

| Substance | Acute toxicity in mice $LD_{50}$ mg/kg s.c. | $LD_{50}$ mg/kg p.o. |
|---|---|---|
| GF 53 | 941 | 1408 |
| GF 61 | 250 | 600 |
| GF 48 | 70 | 200 |
| GF 49 | 400 | 400 |
| GF 52 | 80 | 200 |
| GF 57 | 250 | 300 |
| Imipramine | 385 | 412 |
| Amitriptyline | 126 | 280 |
| Benztropine | 70 | 75 |

We claim:

1. A 3-substituted 4-phenylpiperidine of the formula




(I)

wherein:

R represents alkyl of 1–4 carbon atoms; alkynyl of 2–4 carbon atoms; phenyl; phenyl substituted by alkyl of one to four carbon atoms, alkoxy of one to four carbon atoms, alkylthio of one to four carbon atoms, halogen, nitro, acetylamino, methylsulfonyl, or by methylenedioxo; or tetrahydronaphthyl;

$R^1$ represents hydrogen; alkyl of 1–4 carbon atoms; alkynyl of 2–4 carbon atoms; or 2,2,2-trifluoroethyl;

X represents hydrogen; alkyl or 1–4 carbon atoms; trifluoromethyl; methoxy; halogen; hydroxy; methylthio; or benzyloxy;

and a salt thereof with a pharmaceutically acceptable acid.

2. A compound according to claim 1, in which R is phenyl.

3. A compound according to claim 1, in which R is 4-methoxyphenyl.

4. A compound according to claim 1, in which R is 1,3-benzdioxolyl.

5. The compound according to claim 1, in which R is phenyl, $R^1$ is methyl, and X is hydrogen.

6. The compound according to claim 1, in which R is 4-methoxyphenyl, $R^1$ is methyl, and X is hydrogen.

7. The compound according to claim 1, in which R is 1,3-benzdioxolyl-5, and $R^1$ and X are hydrogen.

8. The compound according to claim 1, in which R is 1,3-benzdioxolyl-5, $R^1$ is methyl, and X is hydrogen.

* * * * *